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<p>(54) Title: SYSTEM FOR ENHANCING CARDIAC SIGNAL SENSING BY CARDIAC PACEMAKERS THROUGH GENETIC TREATMENT</p> <p>(57) Abstract</p> <p>The present invention provides delivery systems for delivering ion channel protein genetic material to cardiac cells in areas adjacent to where an electrode is to be positioned in a patient's heart to improve or correct the signal to noise ratio of cardiac signals, such as the P-wave. More specifically, there is provided a system for delivering sodium ion channel proteins or nucleic acid molecules encoding sodium ion channel proteins to a site in the heart adjacent to an electrode to increase the expression of the same, thereby enhancing the cardiac signal amplitude and enabling improved sensing of cardiac signals by an implanted pacemaker.</p>			

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SYSTEM FOR ENHANCING CARDIAC SIGNAL SENSING  
BY CARDIAC PACEMAKERS THROUGH GENETIC TREATMENT

**FIELD OF THE INVENTION**

The present invention relates to systems for genetically enhancing cardiac signals for use by cardiac 5 pacemakers and, more particularly, for enhancing the signal to noise ratio of atrial P-waves for improved pacemaker sensing.

**BACKGROUND OF THE INVENTION**

The cardiac pacemaker is a widely used device for 10 treating various cardiac disorders, e.g., sick sinus syndrome, "brady-tachy syndrome" and heart block. The basic function of the pacemaker is to deliver stimulus pulses to one or more of the patient's heart chambers, as and when needed, to initiate cardiac depolarizations and thus 15 maintain a desired heart rate, or to affect improvements in cardiac output for patients in heart failure. In addition to delivering stimulus pulses, another important feature is the sensing of a patient's heartbeat signals, when they occur spontaneously, for purposes of controlling the 20 stimulus pulse delivery. Thus, the demand pacemaker inhibits delivery of a stimulus pulse and resets the pulse generator in the event of sensing a timely spontaneous beat, i.e., a P-wave which is an atrial depolarization, or a QRS, or just R-wave, which is a ventricular depolarization. For

- 2 -

example, an AAI mode pacemaker both paces and senses in just the atrium, and inhibits delivery of a pace pulse if a timely P-wave is sensed. The inhibit operation necessarily depends upon reliably sensing spontaneous P-waves. In a dual 5 chamber pacemaker, both the P-wave and R-wave are sensed. As examples of dual chamber pacemakers, see U.S. Patents 4,920,965; 4,539,991; and 4,554,921, incorporated herein by reference. A particular purpose of the dual chamber pacemaker may be to treat a block condition, where the 10 patient's natural pacemaker is operating normally, causing timely atrial contractions, but the depolarization signal is not efficiently propagated to the ventricle so as to cause a following ventricular contraction. In such a situation, the dual chamber pacemaker is designed to sense the P-wave, and 15 deliver a synchronized ventricular stimulus pulse, i.e., a pulse which stimulates the ventricle after a timed AV delay which approximates the AV delay of a healthy heart. It is seen that reliable sensing of the P-wave is vital to this type of dual chamber pacing.

20 In yet another type of pacemaker operation, the pacemaker operates in what is referred to a VDD mode, meaning that it paces only in the ventricle, but senses both P-waves and R-waves, i.e., has single chamber pacing but dual chamber sensing. The advantage of this mode is that 25 only one lead need be positioned in the patient's heart, since no pacing pulses are delivered to the atrium. The VDD lead has the normal electrode or electrode pair at its distal end, for positioning in the ventricle; and it has a "floating" electrode (or electrode pair) proximal to the tip 30 and positioned so that it is located in the atrium, for sensing the P-wave. See, for example, U.S. Patent No. 5,127,694. However, since such a floating electrode is not necessarily embedded into or positioned adjacent the myocardium, the sensed P-wave is not as strong as for the 35 case where a separate atrial lead is used, and consequently, the reliability of sensing the P-wave is even less.

- 3 -

Atrial sensing is additionally considered to be a significant problem because of the low P-wave amplitudes commonly available and the presence of relatively large far field QRS and other "noise" signals. It is commonly accepted that atrial P-wave amplitudes are relatively low compared to ventricular R-waves because of the differences in muscle mass near the electrodes. That is, ventricular R-waves are large because there is a large volume of myocardium around the electrode, whereas the atrial signal is small because the underlying tissue is relatively thin. Thus, for any pacing system which senses the P wave, such as an AAI pacer or any dual sense mode pacer, reliably sensing P-waves is a major problem for which improvement has long been sought.

With regard to the source of the P-wave, it is noted that it is not the muscle itself that is sensed, but the electric potentials resulting from the depolarization of several myocardial cells, i.e., a net positive ion flow into myocardial cells through specialized membrane proteins called voltage-gated ion channels, such as the sodium channels. More muscle mass means there are more membrane channels in the area adjacent to the electrodes. However, the muscle mass adjacent to the atrial electrode cannot be increased. But the P-wave could be enhanced if the number of conducting membrane channels within the adjacent muscle mass can be increased. Sodium channels are transmembrane proteins responsible for the rapid transport of  $\text{Na}^+$  ions across cell membranes underlying the depolarization of the action potential in many types of cells. In particular, cardiac fast sodium channels are responsible for the fast upstroke or phase 0 of the action potential in myocardial cells. Fozzard, et al., *Circ. Res.*, 1985, 56, 475-485. Recently, a human cardiac voltage-dependent sodium channel, hH1, has been cloned, sequenced, and functionally expressed. Gellens, et al., *Proc. Natl. Acad. Sci. USA*, 1992, 89, 554-558.

- 4 -

Gene therapy has also recently emerged as a powerful approach to treating a variety of mammalian diseases. Direct transfer of genetic material into myocardial tissue *in vivo* has recently been demonstrated to be an effective method of expressing a desired protein. For example, direct myocardial transfection of plasmid DNA by direct injection into the heart of rabbits and pigs (Gal, et al., *Lab. Invest.*, 1993, 68, 18-25), as well as of rats (Acsadi, et al., *The New Biol.*, 1991, 3, 71-81), has been shown to result in expression of particular reporter gene products. In addition, direct *in vivo* gene transfer into myocardial cells has also been accomplished by directly injecting adenoviral vectors into the myocardium. French, et al., *Circulation*, 1994, 90, 2415-2424, and PCT Publication WO 94/11506.

Pursuant to the above, this invention provides a system for enhancing the cardiac pacemaker atrial and/or ventricular sensing function, i.e., enhancing the signal to noise ratio of cardiac signals, and in particular the sensed P-wave, through concurrent genetic treatment whereby the number of ion channels responsible for depolarization of the atrial or ventricular myocardial cells is increased. Applicants' invention is directed to delivery systems for introducing ion channel protein genetic material into myocardial cells adjacent to or closest to the position of the atrial or ventricular electrode. In any particular application, the genetic material is placed so as to provide maximum benefit for sensing P-waves, or other cardiac signals, with the pacing lead used, i.e., for an AAI pacing system, a lead which is fixated against the atrial wall.

#### SUMMARY OF THE INVENTION

In accordance with the above, a primary purpose of Applicants' claimed invention is to provide delivery systems for enhancing cardiac pacemaker signal sensing. In a particular embodiment, the claimed invention provides delivery systems for enhancing cardiac pacemaker P-wave

- 5 -

sensing. Upon identifying a patient in which the signal to noise ratio for atrial or ventricular sensing is problematic, ion channel protein genetic material is selected such that expression of a selected ion channel protein in cells adjacent to the position of the atrial or ventricle electrode corrects or improves the signal to noise ratio for cardiac signal sensing. Preferably, expression of a selected ion channel protein can improve or correct the signal to noise ratio for cardiac signal sensing in either 10 or both the ventricles and atria of all persons with pacemakers, especially those persons which have been diagnosed with a low signal to noise ratio for P-wave sensing. Improvement or correction of P-wave sensing can be manifested by an increase in the amplitude of the P-wave, or 15 other characteristic of the cardiac signal, thus resulting in an increase of the signal to noise ratio of the signal sensed in the pacemaker atrial sensing channel. Delivery of the ion channel protein genetic material can be accomplished by adaptation of available pacing leads, such as, for 20 example, AAI or DDD leads, as well as by specific modification of leads and catheters. Delivery of the genetic material may be affected by a pump or may be passive.

The ion channel protein genetic material used in 25 the system and method of this invention comprises recombinant nucleic acid molecules comprising a nucleic acid molecule encoding the ion channel protein inserted into a delivery vehicle, such as, for example, plasmids or adenoviral vectors, and the appropriate regulatory elements. 30 Alternatively, the ion channel protein genetic material comprises the ion channel protein itself. Expression of the desired ion channel protein from recombinant nucleic acid molecules is controlled by promoters, preferably cardiac tissue-specific promoter-enhancers, operably linked to the 35 nucleic acid molecule encoding the ion channel protein. The conduction protein is preferably a sodium ion channel protein, such as, for example, the voltage-dependent sodium

channel hH1, which is used to correct or improve the signal to noise ratio of cardiac signals, and in particular, atrial P-wave sensing. The ion channel protein genetic material is delivered to specific sites adjacent to the atrial or 5 ventricular electrode within the heart by perfusion or injection of a therapeutically effective amount, which is that amount which corrects or improves the signal to noise ratio of the cardiac signal of the myocardial cells adjacent to the electrode. The therapeutically effective amount can 10 be delivered to the specific site in the heart in a single dose or multiple doses, as desired.

The present invention provides a delivery system for delivering a therapeutically effective amount of a predetermined ion channel protein genetic material to an 15 identified cardiac location adjacent the atrial or ventricular electrode, the genetic material being selected for amplifying the particular cardiac signal, such as, for example, the P-wave, from cardiac cells to which it is delivered, thus improving or correcting the cardiac signal 20 to noise ratio received by the sensing electrode. The delivery system includes the selected genetic material contained in a reservoir, and a catheter or electrode subsystem for delivering the genetic material from the reservoir to the identified cardiac location so as to 25 contact a plurality of cells in the proximity of the sensing electrode.

The delivery system may utilize an external reservoir for providing the genetic material, or alternately may utilize an implantable reservoir. In either embodiment, 30 a controllable pump mechanism may be provided for transferring therapeutic doses of the genetic material from the reservoir, through a catheter or electrode, and to the selected cardiac location. The pump may be a mini or micro pump located within the delivery system. Alternatively, 35 rather than using a pump mechanism, the ion channel protein genetic material can be passively delivered to the appropriate location adjacent the appropriate electrode.

- 7 -

The catheter subsystem may be of a type for direct introduction into the myocardium, as with a transthoracic procedure, or, more preferably, a endocardial catheter having a distal tip portion adapted for positioning and 5 injecting the genetic material into the myocardium from within a heart chamber. In a preferred embodiment, the catheter distal tip has a normally withdrawn helical needle, which is extendable when positioned in the vicinity of the selected site so as to be screwed into the heart. The 10 needle is hollow and connects with the catheter lumen so as to receive the pumped genetic material; it has one or more ports located so as to effectively release the genetic material for transduction into the cardiac area adjacent the sensing electrode. In the case of an electrode subsystem, 15 an implantable electrode is used in place of the catheter subsystem, which is able to deliver drugs, such as steroids, or other bioactive agents, such as, for example, ion channel protein genetic material. Such implantable electrodes with drug dispensing capabilities are set forth in U.S. Patents 20 4,711,251, 5,458,631, 4,360,031, and 5,496,360, each of which are incorporated herein by reference. The delivery system can be used for one treatment and then removed, or can be implanted for subsequent treatments, in which latter case it is controllable by an external programmer type 25 device. In another embodiment, the catheter or electrode subsystem may be combined with a pacing lead for sensing the patient's cardiac signals and for providing stimulus pulses.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram presenting the primary 30 steps involved in the practice of this invention, including selecting an appropriate genetic material, positioning delivery system against the heart wall, and expressing the genetic material in an appropriate dose into the determined location.

35 Figure 2 is a schematic representation of a delivery system in accordance with this invention,

- 8 -

illustrating delivery of genetic material into a patient's heart at the chosen location using a catheter subsystem.

Figure 3 is a schematic drawing of the distal portion of a catheter which can be used for injecting a 5 solution carrying chosen genetic material into a patient's heart.

Figure 4 illustrates the distal end of a catheter, having a distal portion which encloses an osmotic pump.

Figure 5A is a schematic representation of a 10 delivery system in accordance with this invention, having a combined catheter and pacing lead, with a separate pump; Figure 5B is another embodiment of a combined pacing lead and delivery catheter having a reservoir located at the distal end of the catheter.

#### 15 DESCRIPTION OF THE PREFERRED EMBODIMENTS

Applicants' invention provides delivery systems for correcting or improving cardiac signal sensing, especially the signal to noise ratio of the atrial P-wave, thus enhancing pacemaker sensing. A problematic signal to 20 noise ratio for P-waves results from a naturally low amplitude P-wave generated in the atrium, noise from the ventricular QRS complex, muscle noise, noise from other sources, or a combination thereof. The signal to noise ratio is determined by routine and conventional techniques known to the skilled artisan. Once the specific problem has 25 been identified in a particular patient, e.g., in any patient with a pacemaker or who is to receive a pacemaker, ion channel protein genetic material is selected such that expression of a selected ion channel protein corrects or 30 improves the cardiac signal amplitude, thus improving or correcting the cardiac signal to noise ratio. The ion channel protein genetic material comprises either the ion channel protein itself or recombinant nucleic acid molecules comprising a nucleic acid molecule encoding the ion channel 35 protein inserted into a delivery vehicle, such as, for example, plasmid, cosmid, YAC vector, viral vectors, and the

like, and the appropriate regulatory elements. In preferred embodiments of the present invention, the nucleic acid molecule encoding the ion channel protein is the full length coding sequence cDNA of an ion channel protein, and is 5 inserted into a plasmid or adenoviral vector, such as, for example, pGEM3 or pBR322, and Ad5, respectively. The regulatory elements are capable of directing expression in mammalian cells, specifically human cells. The regulatory elements include a promoter and a polyadenylation signal.

10 Expression of the desired ion channel protein is preferably controlled by cardiac tissue-specific promoter-enhancers, operably linked to the nucleic acid molecule encoding the ion channel protein. The ion channel protein is preferably a sodium channel protein, such as, for example, the hH1

15 voltage-regulated sodium channel, which is used to correct or improve the cardiac signal to noise ratio. The ion channel protein genetic material is preferably delivered in a pharmaceutical composition comprising, for example, the ion channel protein genetic material in a volume of

20 phosphate-buffered saline with 5% sucrose. In some embodiments, the ion channel protein genetic material is delivered with genetic material encoding the  $\text{Na}^+/\text{K}^+$  pump, which is also inserted into an appropriate delivery vehicle. The ion channel protein genetic material may also be

25 delivered separately or in combination with class I and class IV antiarrhythmic drugs, which have been shown to increase sodium channel mRNA expression. The ion channel protein genetic material is delivered to specific sites within the heart, adjacent to the atrial or ventricular

30 electrode, by perfusion or injection of a therapeutically effective amount, which is that amount which corrects or improves the cardiac signal to noise ratio. Preferably, the therapeutically effective amount corrects or improves the P-wave signal to noise ratio. The therapeutically effective

35 amount can be delivered to the specific site in the heart in single or multiple doses, as desired, using the delivery systems of the invention.

- 10 -

The present invention comprises a delivery system for delivering a therapeutically effective amount of ion channel protein genetic material to a specific cardiac location, adjacent the atrial or ventricular electrode, in 5 such a way as to enhance the amplitude of the cardiac signal, thus improving or correcting the signal to noise ratio. In a first embodiment, the delivery system basically comprises a reservoir subsystem for holding the genetic material, and a catheter subsystem in communication with the 10 reservoir subsystem for placement of the genetic material in and around the identified cardiac location. In another embodiment, the delivery system basically comprises a reservoir subsystem for holding the genetic material, and a electrode subsystem in communication with the reservoir 15 subsystem for placement of the genetic material in and around the identified cardiac location. As seen in the following discussion of several preferred embodiments, the reservoir subsystem and catheter subsystem or electrode subsystem may be separate, or they may be combined.

20 Preferably the reservoir contains up to 25 ml of a genetic material for delivery to the myocardium. In some applications, only a bolus of about 0.1-10 ml, or more preferably 1-5 ml, is delivered to the targeted areas. In other applications, such as where ion channel protein is 25 being delivered in repeated doses, 25 ml or more may be used. Also, the genetic material may be diluted in a saline solution, such as, for example, phosphate-buffered saline (PBS), the reservoir holding the diluted solution for controlled delivery. Additionally, it is to be understood 30 that the reservoir and associated control apparatus may be either implantable or external to the body, depending upon the circumstances, e.g., whether metered doses are to be administered to the patient over a period of time, or whether the delivery of the genetic material is essentially 35 a one time treatment.

Referring now to Fig. 1, the primary steps involved in the practice of this invention are shown in the

- 11 -

flow diagram. The illustrated steps are performed following the initial diagnosis of a patient with a problematic P-wave signal to noise ratio, which can result from a low amplitude P-wave generated in the atrium, noise from the ventricular 5 QRS complex, noise from other sources, or a combination thereof. Diagnosis can be accomplished, for example, by electrocardiography procedures. Preferably, the steps are performed in connection with all patients having cardiac pacemakers. As illustrated in block 30, the next step is to 10 select the appropriate ion channel protein genetic material. This selection yields the "preselected genetic material." The ion channel protein genetic material is next prepared, as illustrated in block 31, by either inserting the nucleic acid molecules encoding the appropriate ion channel protein 15 into a delivery vehicle with the appropriate regulatory elements, in the case of a recombinant nucleic acid molecule, or expressing the ion channel protein from an expression vector, in the case of the ion channel protein itself. As shown in block 32, the next step is to prepare 20 and load the delivery system with a therapeutically effective amount of the ion channel protein genetic material. As illustrated in block 33, the next step comprises inserting the catheter, or other delivery subsystem, such as, for example, the electrode subsystem, 25 into the patient's heart and positioning it against the heart wall. As shown in block 34, the next step comprises administering the therapeutically effective amount to the patient by contacting the appropriate location in the heart, adjacent to the atrial or ventricular electrode, using the 30 delivery system described herein. An alternative method of administering the therapeutically effective amount of the ion channel protein genetic material is to directly inject the heart of the patient. The next step, shown in block 35, is to pace the patient in a standard manner, e.g., dual 35 chamber synchronous pacing which includes sensing the patient's P-waves and delivering synchronized ventricular stimulus pulses, or AAI pacing. In accordance with this

- 12 -

step, it may be preferable to adjust the sensitivity of the atrial or ventricular sensing channel in accordance with the observed cardiac signal amplitude. The final step 36, which is optional, is to evaluate the response of the patient to the treatment by, for example, measuring the amplitude of the cardiac signal, such as, for example, the P-wave, by conventional electrocardiographic techniques, such as, for example, by telemetry from the implanted pulse generator.

The sensitivity can then be adjusted accordingly.

10 Referring now to Fig. 2, there is shown an illustrative embodiment of a delivery system useful for certain applications of this invention, e.g., where larger amounts of genetic material alone or in solution are employed. A catheter 38, preferably a transvenous catheter, 15 includes an elongated catheter body 40, suitably an insulative outer sheath which may be made of polyurethane, Teflon, silicone, or any other acceptable biocompatible plastic. The catheter has a standard lumen (illustrated in Fig. 3) extending therethrough for the length thereof, which 20 communicates through to a hollow helical needle element 44, which is adapted for screwing into the patient's myocardium. The outer distal end of helical element 44 is open or porous, thus permitting genetic material in fluid form to be dispensed out of the end, as is discussed in more detail 25 below in connection with Fig. 3. At the proximal end of the catheter, a fitting 46 is located, to which a Luer lock 48 is coupled. Luer lock 48 is coupled to the proximal end of sheath 40 and receives the lumen. A swivel mount 50 is mounted to Luer lock 48, allowing rotation of the catheter 30 relative to Luer lock 52. Luer lock 52 in turn is coupled through control element 54 to a tube 58 which communicates with reservoir 55, suitably through flow control 57 and filter 56. Reservoir 55 holds a supply of the selected genetic material. Control elements 57 and 54 are used for 35 adjustment of the pressure and flow rate, and may be mechanically or electronically controlled. Thus, unit 54 or 57 may be used to control either rate of delivery, or dosage

- 13 -

size, or both. Control unit 54 may be programmed to automatically release predetermined doses on a timed basis.

Further, for an implanted system, control unit 54 may be activated from an external programmer as illustrated at 53.

5 Reference is made to international application published under the PCT, International Publication No. WO 95/05781, incorporated herein by reference, for a more detailed description of such a reservoir and catheter combination. It is to be understood that such a system is useful for this 10 invention primarily for applications where larger fluid amounts are to be expressed, e.g., where a diluted saline solution is used to wash or perfuse a selected area.

Referring now to Fig. 3, there is shown in expanded detail a schematic of the distal end of the 15 catheter of Fig. 2, illustrating the interconnection of the helical element 44 with the interior of the catheter. As illustrated, the helical needle 44 is provided with an internal lumen 59 which is in communication with the internal lumen 63L of the lead formed by tube 63. In this 20 embodiment, helical element 44 may also be a pacing electrode, in which case it is formed of conductive material and welded, or otherwise fastened, to tip element 61. Tip element 61 in turn is electrically connected to coil or coils 64, 65, which extend the length of the lead and are 25 connected to a pacemaker. An outer membrane 60 forms the outer wall of elongated catheter body 40, shown in Fig. 2. Further referring to Fig. 3, element 44 has an outlet 75 where the genetic material may be expressed, and holes or ports 76, 77, and 78 may also be utilized for providing 30 exits for the genetic material which is supplied through lumen 59 under a suitable pressure of zero up to about one atmosphere from reservoir 55 (shown in Fig. 2) and the control elements.

In practice, a catheter 38 of the form illustrated 35 in Figs. 2 and 3 is advanced to the desired site for treatment, eg, adjacent the site where the sensing electrode is to be positioned. The catheter may be guided to the

- 14 -

indicated location by being passed down a steerable or guidable catheter having an accommodating lumen, for example as disclosed in U.S. Patent No. 5,030,204; or by means of a fixed configuration guide catheter such as illustrated in 5 U.S. Patent No. 5,104,393. Alternately, the catheter may be advanced to the desired location within the heart by means of a deflectable stylet, as disclosed in PCT Patent Application WO 93/04724, published March 18, 1993, or by a deflectable guide wire as disclosed in U.S. Patent No. 10 5,060,660. In yet another embodiment, the helical element 44 may be ordinarily retracted within a sheath at the time of guiding the catheter into the patient's heart, and extended for screwing into the heart by use of a stylet. Such extensible helical arrangements are well known in the 15 pacing art, and are commercially available.

It is to be understood that other forms of the reservoir subsystems and catheter subsystems are within the scope of this invention. Reservoir embodiments include, for example, drug dispensing irrigatable electrodes, such as 20 those described in U.S. Patent 4,360,031; electrically controllable, non-occluding, body implanting drug delivery system, such as those described in U.S. Patent No. 5,041,107; implantable drug infusion reservoir such as those described in U.S. Patent No. 5,176,641; medication delivery 25 devices such as those described in U.S. Patent 5,443,450; infusion pumps, such as SYNCHROMED® made by Medtronic, Inc.; and osmotic pumps, such as those made by Alza.

Referring now to Fig. 4, there is shown, by way of illustration, another embodiment of a delivery system having 30 a combined catheter and reservoir, useful for applications involving delivery of a relatively small bolus of genetic material, e.g., 1-5 ml. Fig. 4 illustrates the distal end of a catheter, having a distal portion 70 which encloses an osmotic pump. See U.S. Patent 4,711,251, assigned to 35 Medtronic, Inc., incorporated herein by reference. The pump includes an inner chamber 68 and an outer chamber 66, which chambers are separated by an impermeable membrane 67. A

- 15 -

semi-permeable outer membrane 72 forms the outer wall of chamber 66. The tubular portion 74 of the helical member connects to lumen 74L within inner chamber 68. A conductor 80, which runs the length of the catheter, extends into the 5 inner chamber 68 and connects with extension 74E as shown at 74C to provide electrical contact through to element 44, in an application which the element 44 is used as a pacing electrode. A insulating cover 86 encompasses the conductor 80 from the point of contact with the semi-permeable outer 10 membrane 72 distally. A seal 79 is provided at the point where the conductor passes through outer membrane 72 and inner membrane 67. An end cap 73, which may be integral with outer membrane 72 closes the chamber. Alternately, end cap 73 may be constructed to elute a predetermined 15 medication, such as, for example, steroids. Steroids, such as dexamethasone sodium phosphate, beclamethasone, and the like, are used to control inflammatory processes.

In this arrangement, prior to inserting the catheter distal end into the patient's heart, the inner 20 chamber 68 is charged with the genetic material which is to be dispensed into the myocardium. This may be done, for example, by simply inserting a micro needle through end cap 73, and inserting the desired bolus of genetic material into chamber 68. After the chamber 68 is filled and the is 25 catheter is implanted, body fluids will enter chamber 66 through membrane 72 to impart a pressure on the inner chamber 68 via the impermeable membrane 67. This results in a dispensing of the genetic material stored within chamber 68 through the lumen 74L of extension 74E and through the 30 outlet 75 of the helical element 44. Although the preferred needle or element 44 is helical, additional configurations of needles or elements can also be used as known to those skilled in the art.

Still referring now to Fig. 4, there is 35 illustrated another embodiment of a catheter tip useful for delivering a small bolus of the selected genetic material. In this embodiment, the bolus of material is stored within

- 16 -

the hollow interior of distal needle 44, i.e., the interior is the reservoir. The interior reservoir is maintained sealed by use of a soluble material which is normally solid, but which dissolves when subjected to body fluids for a period of time. An example of such material is mannitol. Plugs or globules 81-85 of mannitol are illustrated (by dashed lines) in place to block the two ends of element 44, as well as the ports 76, 77, 78. This may be combined with an osmotic pump, as described in connection with Fig. 3, where the outer chamber is filled with a saline solution which forces the genetic material out of the ports of element 44. Another alternate embodiment, not shown, is to use a stylet which inserted through to the distal end of the catheter, to push a piston which aids in expressing the genetic material into the myocardial cells. Alternatively, the piston can be driven by a micro pump. In another embodiment, the genetic material contacts the myocardial cells by passive delivery.

Referring now to Fig. 5A, there is shown, by way of illustration, another embodiment of an implantable delivery system comprising a combined pacing lead and delivery catheter, hereinafter referred to simply as a catheter. In this embodiment, the catheter 90 is combined with a pacemaker or pulse generator (not shown) and a source of genetic material such as illustrated by pump 92 which is suitably implanted near the pacemaker. The proximal end 91 of the catheter is connected to the pacemaker in the standard fashion. The genetic material is delivered through connecting tube 93 to a proximal section 88 of the catheter, communicating with lengthwise catheter lumen illustrated at 89. Alternately, the pacemaker head may contain a reservoir and micropump, for providing delivery of the genetic material directly to the lumen 89. The main length of the catheter has an outside sheath of biocompatible insulating material 96, and at least one conductor coil 95 which communicates electrically from the pacemaker to electrode 97 at the distal tip of the catheter. The catheter further

- 17 -

comprises an axially positioned polymeric cannula 94, having lumen 87, through at least a portion of the catheter length and positioned within coil 95, which provides an inner surface for the catheter lumen. The cannula terminates at 5 the distal end of the catheter, just proximal to the tip portion of electrode 97, which is illustrated as having an outer porous surface. Electrode 97 has a central opening, shown covered with the porous electrode material, through which genetic material can pass when the catheter is 10 positioned in the patient. As shown, conductor coil 95 is electrically connected to electrode 97, and connects pace pulses and sensed cardiac signals between the pacemaker and the electrode. Of course, for a bipolar embodiment, the lead/catheter 90 carries a second electrode (not shown), 15 suitably a ring electrode just proximal to electrode 97. Also, as illustrated, a fixation mechanism such as tines 98 are employed for fixing or anchoring the distal tip to the heart wall of the patient.

In one embodiment, pump 92 is suitably an osmotic 20 minipump, which pumps fluid contained within tube 93, into catheter portion 88 and through the lumens 89, 87 to the tip electrode 97. As mentioned previously, the reservoir and pump may alternately be mounted in the pacemaker device itself. In either instance, the genetic 25 material is delivered under very minimal pressure from the reservoir through the lumen of the catheter to the electrode; where it is passed through the electrode central channel to contact myocardial cells. In yet another embodiment, the lumen portion 87 provided by the cannula is 30 utilized as the reservoir. In this embodiment, delivery may either be passive, or with the aid of a micropump (not shown). The genetic material can be preloaded into the cannula, or it can be inserted by a needle just before the catheter is introduced and positioned with the patient.

35 In another embodiment, as illustrated in Figure 5B, a chamber 99 is provided just proximal from eluting electrode 97, and serves as the reservoir of the genetic

- 18 -

material. Insulating material 96 is formed from a self-sealing material such that it may be pierced with a needle, or the like, and reseal itself, thus allowing introduction of the genetic material into the chamber prior to

5 implantation. Alternately, insulating material 96 can contain a port (not shown) through which the needle inserts the genetic material. In this embodiment, delivery of the material is without a pump, i.e., passive, the material draining slowly through the microporous portion of electrode

10 97.

The above described delivery systems can be used, for example, in methods of pacing and enhancing the detectability of sensed cardiac signals. A supply of a genetic material of the class having the property of 15 increasing the expression of ion channels in cardiac cells to which it is delivered is selected. A transvenous catheter, having proximal and distal ends and a pacing electrode at the distal end, is introduced into the patient. The distal end of the catheter is positioned against the 20 patient's heart wall and the genetic material is delivered through the catheter and out of the distal end, to the cardiac cells adjacent the pacing electrode, thereby enhancing cardiac signals produced by the cells. Normal cardiac pacing is carried out with the pacemaker and 25 connected catheter implanted in the patient.

Although a transvenous form of delivery system is preferred, it is to be understood that the invention can employ other methods and devices. For example, a small bolus of selected genetic material can be loaded into a 30 micro-syringe, e.g., a 100  $\mu$ l Hamilton syringe, and applied directly from the outside of the heart.

As used herein, the phrase "cardiac signal" refers to any cardiac signal that is detectable and includes, but is not limited to, the P-wave.

35 As used herein, the phrase "signal to noise ratio" refers to the ratio of the amplitude of the cardiac signal, such as, for example, the P-wave, to the amplitude of the

- 19 -

"noise." In addition, the signal to noise ratio can be measured for other cardiac signals as well. Sources of "noise" include, but are not limited to, the QRS complex and muscle noise. It is desirable to establish a high signal to 5 noise ratio, i.e., a signal to noise ratio of greater than 1:1 for unipolar leads and greater than 3:1 for bipolar leads. It is even more preferred to establish a signal to noise ratio greater than 10:1.

As used herein, the phrase "ion channel protein 10 genetic material" refers to recombinant nucleic acid molecules encoding an ion channel protein or, alternatively, an ion channel protein itself, which is used in the methods and delivery systems of the invention. For chronic treatment, or long term treatment, the ion channel protein 15 genetic material will be in the form of recombinant nucleic acid molecules encoding the ion channel protein. In contrast, for acute treatment, or short term treatment, the ion channel protein genetic material will be in the form of the ion channel proteins themselves.

20 A "recombinant nucleic acid molecule", as used herein, is comprised of an isolated ion channel protein-encoding nucleotide sequence inserted into a delivery vehicle. Regulatory elements, such as the promoter and polyadenylation signal, are operably linked to the 25 nucleotide sequence encoding the ion channel protein, whereby the protein is capable of being produced when the recombinant nucleic acid molecule is introduced into a cell.

The nucleic acid molecules encoding the ion 30 channel proteins are prepared synthetically or, preferably, from isolated nucleic acid molecules, as described below. A nucleic acid is "isolated" when purified away from other cellular constituents, such as, for example, other cellular nucleic acids or proteins, by standard techniques known to those of ordinary skill in the art. The coding region of 35 the nucleic acid molecule encoding the ion channel protein can encode a full length gene product or a subfragment thereof, or a novel mutated or fusion sequence. The protein

coding sequence can be a sequence endogenous to the target cell, or exogenous to the target cell. The promoter, with which the coding sequence is operably associated, may or may not be one that normally is associated with the coding sequence:

The nucleic acid molecule encoding the ion channel protein is inserted into an appropriate delivery vehicle, such as, for example, an expression plasmid, cosmid, YAC vector, and the like. Almost any delivery vehicle can be used for introducing nucleic acids into the cardiovascular system, including, for example, recombinant vectors, such as one based on adenovirus serotype 5, Ad5, as set forth in French, et al., *Circulation*, 1994, 90, 2414-2424, which is incorporated herein by reference. An additional protocol for adenovirus-mediated gene transfer to cardiac cells is set forth in WO 94/11506, Johns, *J. Clin. Invest.*, 1995, 96, 1152-1158, and in Barr, et al., *Gene Ther.*, 1994, 1, 51-58, both of which are incorporated herein by reference. Other recombinant vectors include, for example, plasmid DNA vectors, such as one derived from pGEM3 or pBR322, as set forth in Acsadi, et al., *The New Biol.*, 1991, 3, 71-81, and Gal, et al., *Lab. Invest.*, 1993, 68, 18-25, both of which are incorporated herein by reference, cDNA-containing liposomes, artificial viruses, nanoparticles, and the like. It is also contemplated that ion channel proteins be injected directly into the myocardium.

The regulatory elements of the recombinant nucleic acid molecules of the invention are capable of directing expression in mammalian cells, specifically human cells. The regulatory elements include a promoter and a polyadenylation signal. In addition, other elements, such as a Kozak region, may also be included in the recombinant nucleic acid molecule. Examples of polyadenylation signals useful to practice the present invention include, but are not limited to, SV40 polyadenylation signals and LTR polyadenylation signals. In particular, the SV40 polyadenylation signal which is in pCEP4 plasmid

- 21 -

(Invitrogen, San Diego, CA), referred to as the SV40 polyadenylation signal, can be used.

The promoters useful in constructing the recombinant nucleic acid molecules of the invention may be 5 constitutive or inducible. A constitutive promoter is expressed under all conditions of cell growth. Exemplary constitutive promoters include the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase,  $\beta$ -actin, human 10 myosin, human hemoglobin, human muscle creatine, and others. In addition, many viral promoters function constitutively in eukaryotic cells, and include, but are not limited to, the early and late promoters of SV40, the Mouse Mammary Tumor Virus (MMTV) promoter, the long terminal repeats (LTRs) of 15 Maloney leukemia virus, Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV) immediate early promoter, Epstein Barr Virus (EBV), Rous Sarcoma Virus (RSV), and other retroviruses, and the thymidine kinase promoter of herpes simplex virus. Other promoters are known to those of 20 ordinary skill in the art.

Inducible promoters are expressed in the presence of an inducing agent. For example, the metallothionein promoter is induced to promote (increase) transcription in the presence of certain metal ions. Other inducible 25 promoters are known to those of ordinary skill in the art.

Promoters and polyadenylation signals used must be functional within the cells of the mammal. In order to maximize protein production, regulatory sequences may be selected which are well suited for gene expression in the 30 cardiac cells into which the recombinant nucleic acid molecule is administered. For example, the promoter is preferably a cardiac tissue-specific promoter-enhancer, such as, for example, cardiac isoform troponin C (cTNC) promoter. Parmacek, et al., *J. Biol. Chem.*, 1990, 265, 15970-15976, 35 and Parmacek, et al., *Mol. Cell Biol.*, 1992, 12, 1967-1976. In addition, codons may be selected which are most efficiently transcribed in the cell. One having ordinary

skill in the art can produce recombinant nucleic acid molecules which are functional in the cardiac cells.

Genetic material can be introduced into a cell or "contacted" by a cell by, for example, transfection or

5 transduction procedures. Transfection refers to the acquisition by a cell of new genetic material by incorporation of added nucleic acid molecules. Transfection can occur by physical or chemical methods. Many transfection techniques are known to those of ordinary skill 10 in the art including: calcium phosphate DNA co-precipitation; DEAE-dextran DNA transfection; electroporation; naked plasmid adsorption, and cationic liposome-mediated transfection. Transduction refers to the process of transferring nucleic acid into a cell using a DNA 15 or RNA virus. Suitable viral vectors for use as transducing agents include, but are not limited to, retroviral vectors, adeno associated viral vectors, vaccinia viruses, and Semliki Forest virus vectors.

Treatment of cells, or contacting cells, with 20 recombinant nucleic acid molecules can take place *in vivo* or *ex vivo*. For *ex vivo* treatment, cells are isolated from an animal (preferably a human), transformed (i.e., transduced or transfected *in vitro*) with a delivery vehicle containing a nucleic acid molecule encoding an ion channel protein, and 25 then administered to a recipient. Procedures for removing cells from mammals are well known to those of ordinary skill in the art. In addition to cells, tissue or the whole or parts of organs may be removed, treated *ex vivo* and then returned to the patient. Thus, cells, tissue or organs may 30 be cultured, bathed, perfused and the like under conditions for introducing the recombinant nucleic acid molecules of the invention into the desired cells.

For *in vivo* treatment, cells of an animal, preferably a mammal and most preferably a human, are 35 transformed *in vivo* with a recombinant nucleic acid molecule of the invention. The *in vivo* treatment may involve systemic intravenous treatment with a recombinant nucleic

acid molecule, local internal treatment with a recombinant nucleic acid molecule, such as by localized perfusion or topical treatment, and the like. When performing *in vivo* administration of the recombinant nucleic acid molecule, the preferred delivery vehicles are based on noncytopathic eukaryotic viruses in which nonessential or complementable genes have been replaced with the nucleic acid sequence of interest. Such noncytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have recently been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for high-efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell line with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M. "Gene Transfer and Expression, a Laboratory Manual", W.H. Freeman Co., New York (1990) and Murry, E.J. e.d. "Methods in Molecular Biology", Vol. 7, Humana Press, Inc., Clifton, New Jersey (1991).

A preferred virus for contacting cells in certain applications, such as in *in vivo* applications, is the adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus can be engineered to be replication deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as heat and lipid solvent stability, high transduction frequencies in cells of diverse lineages, including hemopoietic cells, and lack of superinfection inhibition thus allowing multiple

- 24 -

series of transductions. Recent reports indicate that the adeno-associated virus can also function in an extrachromosomal fashion.

In preferred embodiments of the present invention, 5 the recombinant nucleic acid molecules comprising nucleic acid molecules encoding the ion channel proteins, or, in the alternative, the ion channel proteins, are delivered to cardiac cells adjacent the atrial or ventricular electrode, or both, using the delivery systems set forth above. 10 Alternatively, the ion channel protein genetic material is delivered to the cardiac cells by direct injection.

In preferred embodiments of the present invention, the nucleic acid molecules encoding the ion channel proteins comprise the full length coding sequence cDNA of an ion 15 channel protein. Preferably, the ion channel proteins are sodium channel proteins; more preferably, the ion channel protein is the voltage-regulated sodium channel hH1. Such a nucleic acid molecule is described in the Gellens, et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 554-558, and White, et 20 al., Mol. Pharmacol., 1991, 39, 604-608 references, both of which are incorporated herein by reference, which contain the full length amino acid sequence and cDNA sequence, respectively.

Introduction of the ion channel-encoding nucleic 25 acid molecules or the ion channel proteins to cardiac cells adjacent the atrial or ventricular electrode will result in increased expression of sodium channels, producing a larger cardiac signal, such as, for example, P-wave, and thus, an improved or corrected signal to noise ratio.

30 Nucleic acid molecules comprising nucleotide sequences encoding hH1 sodium channel are isolated and purified according to the methods set forth in Gellens, et al., Proc. Natl. Acad. Sci. USA, 1992, 89, 554-558, and White, et al., Mol. Pharmacol., 1991, 39, 604-608. The 35 nucleic acid and protein sequences of hH1 sodium channel are set forth in SEQ ID NO:1 and SEQ ID NO:2, respectively. It is contemplated that nucleic acid molecules comprising

- 25 -

nucleotide sequences that are preferably at least 70% homologous, more preferably at least 80% homologous, and most preferably at least 90% homologous to the ion channel nucleotide sequences described in SEQ ID NO:1 can also be 5 used.

It is understood that minor modifications of nucleotide sequence or the primary amino acid sequence may result in proteins which have substantially equivalent or enhanced activity as compared to the ion channel proteins 10 exemplified herein. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental such as through mutations in hosts which produce the ion channel proteins. A "mutation" in a protein alters its primary structure (relative to the commonly occurring or 15 specifically described protein) due to changes in the nucleotide sequence of the DNA which encodes it. These mutations specifically include allelic variants. Mutational changes in the primary structure of a protein can result from deletions, additions, or substitutions. A "deletion" 20 is defined as a polypeptide in which one or more internal amino acid residues are absent as compared to the native sequence. An "addition" is defined as a polypeptide which has one or more additional internal amino acid residues as compared to the wild type protein. A "substitution" results 25 from the replacement of one or more amino acid residues by other residues. A protein "fragment" is a polypeptide consisting of a primary amino acid sequence which is identical to a portion of the primary sequence of the protein to which the polypeptide is related.

30 Preferred "substitutions" are those which are conservative, i.e., wherein a residue is replaced by another of the same general type. As is well understood, naturally-occurring amino acids can be subclassified as acidic, basic, neutral and polar, or neutral and nonpolar and/or aromatic. 35 It is generally preferred that encoded peptides differing from the native form contain substituted codons for amino acids which are from the same group as that of the amino

- 26 -

acid replaced. Thus, in general, the basic amino acids Lys, Arg, and Histidine are interchangeable; the acidic amino acids Asp and Glu are interchangeable; the neutral polar amino acids Ser, Thr, Cys, Gln, and Asn are interchangeable; 5 the nonpolar aliphatic acids Gly, Ala, Val, Ile, and Leu are conservative with respect to each other (but because of size, Gly and Ala are more closely related and Val, Ile and Leu are more closely related), and the aromatic amino acids Phe, Trp, and Tyr are interchangeable.

10 While Pro is a nonpolar neutral amino acid, it represents difficulties because of its effects on conformation, and substitutions by or for Pro are not preferred, except when the same or similar conformational results can be obtained. Polar amino acids which represent 15 conservative changes include Ser, Thr, Gln, Asn; and to a lesser extent, Met. In addition, although classified in different categories, Ala, Gly, and Ser seem to be interchangeable, and Cys additionally fits into this group, or may be classified with the polar neutral amino acids.

20 Some substitutions by codons for amino acids from different classes may also be useful.

Once the nucleic acid molecules encoding the ion channel proteins are isolated and purified according to the methods described above, recombinant nucleic acid molecules 25 are prepared in which the desired ion channel nucleic acid molecule is incorporated into a delivery vehicle by methods known to those skilled in the art, as taught in, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Ed. Cold Spring Harbor Press (1989).

30 Preferred delivery vehicles include, for example, plasmids (Acsadi, et al., *The New Biol.*, 1991, 3, 71-81, and Gal, et al., *Lab. Invest.*, 1993, 68, 18-25, both of which are incorporated herein by reference) and adenovirus (WO 94/11506, Johns, *J. Clin. Invest.*, 1995, 96, 1152-1158, and 35 in Barr, et al., *Gene Ther.*, 1994, 1, 51-58, each of which are incorporated herein by reference). The nucleic acid molecules encoding ion channel proteins, or ion channel

proteins produced therefrom, are delivered to the cardiac cells adjacent to the atrial electrode by the delivery systems of the present invention. Thus, such delivery systems of the present invention are used to contact the 5 cardiac cells adjacent the atrial electrode with recombinant nucleic acid molecules encoding an ion channel protein, or ion channel proteins.

Where the ion channel protein genetic material is in the form of ion channel proteins, such proteins can be 10 prepared in large quantities by using various standard expression systems known to those skilled in the art.

Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Ed. Cold Spring Harbor Press (1989), pp. 16.1-16.55, incorporated herein by reference.

15 The recombinant nucleic acid molecules or ion channel proteins are preferably delivered in a pharmaceutical composition. Such pharmaceutical compositions can include, for example, the recombinant nucleic acid molecule or protein in a volume of phosphate- 20 buffered saline with 5% sucrose. In other embodiments of the invention, the recombinant nucleic acid molecule or protein is delivered with suitable pharmaceutical carriers, such as those described in the most recent edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard 25 reference text in this field. The recombinant nucleic acid molecule or protein is delivered in a therapeutically effective amount. Such amount is determined experimentally and is that amount which either improves or corrects the P- wave signal to noise ratio by enhancing the P-wave amplitude 30 as a result of the increased expression of sodium channels in the cardiac cells adjacent the atrial or ventricular electrode. The amount of recombinant nucleic acid molecule or protein is preferably between 0.01  $\mu$ g and 100 mg, more preferably between 0.1  $\mu$ g and 10 mg, more preferably between 35 1  $\mu$ g and 1 mg, and most preferably between 10  $\mu$ g and 100  $\mu$ g. A single therapeutically effective amount is referred to as a bolus. Where adenovirus vectors are used, the amount of

recombinant nucleic acid molecule is preferably between  $10^7$  plaque forming units (pfu) and  $10^{15}$  pfu, more preferably between  $10^8$  pfu and  $10^{14}$  pfu, and most preferably between  $10^9$  pfu and  $10^{12}$  pfu. A single therapeutically effective amount 5 of ion channel protein genetic material is referred to as a bolus. In some embodiments of the present invention, the delivery of the recombinant nucleic acid molecules or proteins is combined with steroid elution, such as with dexamethasone sodium phosphate, beclamethasone, and the 10 like, to control inflammatory processes.

In some embodiments of the invention, it may be preferred to administer, in addition to ion channel protein genetic material, delivery vehicle encoding the  $\text{Na}^+/\text{K}^+$  pump. The  $\text{Na}^+/\text{K}^+$  pump acts to discharge  $\text{Na}^+$  ions from the myocardial 15 cells that have accumulated as a result of the introduction of the ion channel protein genetic material. This treatment can be optional, as determined by the skilled practitioner. cDNA encoding the alpha and beta subunits of the human  $\text{Na}^+/\text{K}^+$  pump are set forth in Kawakami, et al., *J. Biochem.*, 1986, 20 100, 389-397, and Kawakami, et al., *Nuc. Acids Res.*, 1986, 14, 2833-2844, both of which are incorporated herein by reference. The nucleic acid and amino acid sequences for the alpha subunit are set forth in SEQ ID NO:5 and SEQ ID NO:6, respectively. The nucleic acid and amino acid 25 sequences for the beta subunit are set forth in SEQ ID NO:7 and SEQ ID NO:8, respectively. The delivery vehicles for the pump subunits can be constructed from cDNA libraries in the same manner as set forth for hH1, except that the forward primer 5'-ATGGGGAAAGGGGGTTGGACGTGAT-3' (SEQ ID NO:9) 30 and reverse primer 5'-ATAGTAGGTTCTCTCCACCCA-3' (SEQ ID NO:10) for the alpha subunit, and the forward primer 5'-ATGGCCCGCGGGAAAGCCAAGGAG-3' (SEQ ID NO:11) and reverse primer 5'-GCTCTTAACCTCAATTTTACATC-3' (SEQ ID NO:12) for the beta 35 subunit are used. It is understood that other primers can be used in addition to those set forth herein, as is well known to the skilled artisan. A therapeutically effective amount of the genetic material encoding the  $\text{Na}^+/\text{K}^+$  pump is

delivered to the myocardial cells using the delivery systems described herein. The therapeutically effective amount is determined by the practitioner, and depends upon the results achieved with the ion channel protein genetic material.

5 In preferred embodiments of the invention, the recombinant nucleic acid molecules encoding the ion channel proteins is delivered with class I and/or class IV antiarrhythmic drugs, such as, for example, verapamil, mexiletine, and the like, or combinations thereof. These 10 drugs may be delivered subcutaneously, intravenously, injected in the immediate vicinity of the atrial electrode, or as determined by the skilled artisan. These drugs may be delivered by one injection, or in multiple injections. The amount of antiarrhythmic drugs depends upon the age, weight, 15 sex, and other characteristics of the patient, and is determined empirically by the skilled artisan. Class I and/or class IV antiarrhythmic drugs have been shown to enhance sodium ion channel expression in mammals. Duff, et al., *Mol. Pharmacol.*, 1992, 42, 570-574, and Taouis, et al., 20 *J. Clin. Invest.*, 1991, 88, 375-378, both of which are incorporated herein by reference.

The following examples are meant to be exemplary of the preferred embodiments of the invention and are not meant to be limiting.

## 25 EXAMPLES

### Example 1: Isolation and Purification of Nucleic Acid Molecule Encoding hH1

Nucleic acid molecules encoding hH1 are isolated and purified according to general methods well known to 30 those skilled in the art, and in particular, by the method set forth in Gellens, et al., *Proc. Natl. Acad. Sci. USA*, 1992, 89, 554-558, incorporated herein by reference. Briefly, a size selected and random-primed adult human cardiac cDNA library constructed in  $\lambda$ ZAPII (Stratagene) is 35 screened with cDNA probes corresponding to nucleotides 1-4385 and 5424-7076 derived from the rat muscle TTX-I isoform (rSkM2), as set forth in Kallen, et al., *Neuron*, 1990, 4,

- 30 -

233-242, incorporated herein by reference. Hybridizations are performed at 42°C for 18 hours in 50% formamide, 5X SSPE, 5X Denhardt's solution, 0.1% SDS/salmon sperm DNA, random primed <sup>32</sup>P-labeled probe. Filters are washed with 6X 5 standard saline citrate, 0.1% SDS at 65°C. Plaque purified clones are rescued as pBluescript phagemids and sequenced as described in Kallen, et al., *Neuron*, 1990, 4, 233-242. A full-length hH1 construct is made in pBluescript by sequential ligation of S14 *EcoR1-Sac II* (nt +1 to +252), C75 10 *Sac II-KpnI* (nt +253 to +4377), and C92 *KpnI-EcoR1* (nt +4378 to +8491) fragments and the full length insert is moved into a modified pSP64T vector, as set forth in White, et al., *Mol. Pharmacol.*, 1991, 39, 604-608, incorporated herein by reference. Nucleotides -151 to -8 of the 5' untranslated 15 region are deleted from the construct using exonuclease III and mung bean nuclease, as set forth in White, et al., *Mol. Pharmacol.*, 1991, 39, 604-608.

Alternatively, cDNA for hH1 may be prepared from fresh cardiac tissue. Briefly, total cellular RNA is 20 isolated and purified (Chomczynsky, et al., *Anal. Biochem.*, 1987, 162, 156-159) from heart tissue, obtained from cardiac transplantation donors, or from salvaged tissue, and selected for poly(A) RNA (Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Ed. Cold Spring Harbor 25 Press (1989), pp. 7.26-7.29). cDNA corresponding to the hH1 sodium channel protein is prepared from the poly(A) cardiac RNA by reverse transcription using a GENEAMP™ PCR kit (Perkin Elmer Cetus, Norwalk, CT), or the like, using random hexamers according to the manufacturer's instructions. The 30 specific hH1 nucleic acid molecules are amplified by the polymerase chain reaction (PCR), also using the GENEAMP™ PCR kit, or the like, using forward and reverse primers specific for hH1 according to the manufacturer's instructions. For example, the forward primer for cloning hH1 is preferably 35 5'-ATGGCAAACCTCCTATTACCTCGG-3' (SEQ ID NO:3), and the reverse primer is 5'-CACGATGGACTCACGGTCCCTGTC-3' (SEQ ID NO:4). It is understood that additional primers can be used

for amplification as determined by those skilled in the art. These primers may be preceded at the 5' terminus by nucleotide sequences containing endonuclease restriction sites for easy incorporation into vectors. The specific ion 5 channel nucleic acid molecules can also be amplified by PCR from human genomic DNA (Stratagene, San Diego, CA). After cutting the PCR products with the appropriate restriction endonuclease(s), the PCR products are purified by phenol:chloroform extractions, or using commercial 10 purification kits, such as, for example, MAGIC™ Minipreps DNA Purification System (Promega, Madison, WI). The specific nucleotide sequence of the PCR products is determined by conventional DNA sequencing procedures, and the identity of the PCR products confirmed by comparison to 15 the published sequences for the ion channel proteins.

**Example 2: Insertion of Ion Channel cDNA into Delivery Vehicles**

Preferably, ion channel cDNA is inserted into either plasmid or adenoviral vectors. Plasmid vectors 20 include for example, pGEM3 or pBR322, as set forth in Acsadi, et al., *The New Biol.*, 1991, 3, 71-81, and Gal, et al., *Lab. Invest.*, 1993, 68, 18-25. Adenoviral vectors include for example, adenovirus serotype 5, Ad5, as set forth in French, et al., *Circulation*, 1994, 90, 2414-2424, 25 and Johns, *J. Clin. Invest.*, 1995, 96, 1152-1158.

Preferably, the primers used to amplify the ion channel nucleic acid molecules are designed with unique endonuclease restriction sites located at the 5' terminus. In the absence of such design, polylinker arms, containing 30 unique restriction sites, can be ligated thereto. After cutting the purified PCR products with the appropriate restriction endonuclease(s), the plasmid vector, comprising a polylinker, is also cut with the same restriction endonuclease(s), affording the ion channel nucleic acid 35 molecule a site at which to ligate. In a similar manner, recombinant adenovirus (Gluzman, et al., in *Eukaryotic Viral Vectors*, Gluzman, ed., Cold Spring Harbor Press, 1982,

- 32 -

pp.187-192, French, et al., *Circulation*, 1994, 90, 2414-2424, and Johns, *J. Clin. Invest.*, 1995, 96, 1152-1158) containing ion channel cDNA molecules are prepared in accordance with standard techniques well known to those skilled in the art.

5 It is contemplated that variations of the above-described invention may be constructed that are consistent with the spirit of the invention.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANTS: Ken Stokes  
Josée Morissette

(ii) TITLE OF INVENTION: SYSTEMS FOR ENHANCING CARDIAC SIGNAL  
SENSING BY CARDIAC PACEMAKERS THROUGH  
GENETIC TREATMENT

(iii) NUMBER OF SEQUENCES: 12

## (iv) CORRESPONDENCE ADDRESS:

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## (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: WordPerfect 6.1

## (vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: N/A  
(B) FILING DATE: Herewith  
(C) CLASSIFICATION:

## (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Paul K. Legaard  
(B) REGISTRATION NUMBER: 38,534  
(C) REFERENCE/DOCKET NUMBER: MEDT-0082

## (ix) TELECOMMUNICATION INFORMATION:

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## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6048 bases  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATG GCA AAC TTC CTA TTA CCT CGG GGC ACC AGC AGC TTC CGC AGG	45
Met Ala Asn Phe Leu Leu Pro Arg Gly Thr Ser Ser Phe Arg Arg	
1 5 10 15	
TTC ACA CGG GAG TCC CTG GCA GCC ATC GAG AAG CGC ATG GCG GAG	90
Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu	
20 25 30	
AAG CAA GCC CGC GGC TCA ACC ACC TTG CAG GAG AGC CGA GAG GGG	135
Lys Gln Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly	
35 40 45	
CTG CCC GAG GAG GAG GCT CCC CGG CCC CAG CTG GAC CTG CAG GCC	180
Leu Pro Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala	
50 55 60	

- 34 -

TCC AAA AAG CTG CCA GAT CTC TAT GGC AAT CCA CCC CAA GAG CTC	225
Ser Lys Lys Leu Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu	
65 70 75	
ATC GGA GAG CCC CTG GAG GAC CTG GAC CCC TTC TAT AGC ACC CAA	270
Ile Gly Glu Pro Leu Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln	
80 85 90	
AAG ACT TTC ATC GTA CTG AAT AAA GGC AAG ACC ATC TTC CGG TTC	315
Lys Thr Phe Ile Val Leu Asn Lys Gly Lys Thr Ile Phe Arg Phe	
95 100 105	
AGT GCC ACC AAC GCC TTG TAT GTC CTC AGT CCC TTC CAC CCA GTT	360
Ser Ala Thr Asn Ala Leu Tyr Val Leu Ser Pro Phe His Pro Val	
110 115 120	
CGG AGA GCG GCT GTG AAG ATT CTG GTT CAC TCG CTC TTC AAC ATG	405
Arg Arg Ala Ala Val Lys Ile Leu Val His Ser Leu Phe Asn Met	
125 130 135	
CTC ATC ATG TGC ACC ATC CTC ACC AAC TGC GTG TTC ATG GCC CAG	450
Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe Met Ala Gln	
140 145 150	
CAC GAC CCT CCA CCC TGG ACC AAG TAT GTC GAG TAC ACC TTC ACC	495
His Asp Pro Pro Trp Thr Lys Tyr Val Glu Tyr Thr Phe Thr	
155 160 165	
GCC ATT TAC ACC TTT GAG TCT CTG GTC AAG ATT CTG GCT CGA GCT	540
Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile Leu Ala Arg Ala	
170 175 180	
TTC TGC CTG CAC GCG TTC ACT TTC CTT CGG GAC CCA TGG AAC TGG	585
Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp	
185 190 195	
CTG GAC TTT AGT GTG ATT ATC ATG GCA TAC ACA ACT GAA TTT GTG	630
Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu Phe Val	
200 205 210	
GAC CTG GGC AAT GTC TCA GCC TTA CGC ACC TTC CGA GTC CTC CGG	675
Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg	
215 220 225	
GCC CTG AAA ACT ATA TCA GTC ATT TCA GGG CTG AAG ACC ATC GTG	720
Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val	
230 235 240	
GGG GCC CTG ATC CAG TCT GTG AAG AAG CTG GCT GAT GTG ATG GTC	765
Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val	
245 250 255	
CTC ACA GTC TTC TGC CTC AGC GTC TTT GCC CTC ATC GGC CTG CAG	810
Leu Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln	
260 265 270	
CTC TTC ATG GGC AAC CTA AGG CAC AAG TGT GTG CGC AAC TTC ACA	855
Leu Phe Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr	
275 280 285	
GCG CTC AAC GGC ACC AAC GGC TCC GTG GAG GCC GAC GGC TTG GTC	900
Ala Leu Asn Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val	
290 295 300	
TGG GAA TCC CTG GAC CTT TAC CTC AGT GAT CCA GAA AAT TAC CTG	945
Trp Glu Ser Leu Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu	
305 310 315	

- 35 -

CTC AAG AAC GGC ACC TCT GAT GTG TTA CTG TGT GGG AAC AGC TCT	990
Leu Lys Asn Gly Thr Ser Asp Val Leu Leu Cys Gly Asn Ser Ser	
320 325 330	
GAC GCT GGG ACA TGT CCG GAG GGC TAC CGG TGC CTA AAG GCA GGC	1035
Asp Ala Gly Thr Cys Pro Glu Gly Tyr Arg Cys Leu Lys Ala Gly	
335 340 345	
GAG AAC CCC GAC CAC GGC TAC ACC AGC TTC GAT TCC TTT GCC TGG	1080
Glu Asn Pro Asp His Gly Tyr Thr Ser Phe Asp Ser Phe Ala Trp	
350 355 360	
GCC TTT CTT GCA CTC TTC CGC CTG ATG ACG CAG GAC TGC TGG GAG	1125
Ala Phe Leu Ala Leu Phe Arg Leu Met Thr Gln Asp Cys Trp Glu	
365 370 375	
CGC CTC TAT CAG CAG ACC CTC AGG TCC GCA GGG AAG ATC TAC ATG	1170
Arg Leu Tyr Gln Gln Thr Leu Arg Ser Ala Gly Lys Ile Tyr Met	
380 385 390	
ATC TTC TTC ATG CTT GTC ATC TTC CTG GGG TCC TTC TAC CTG GTG	1215
Ile Phe Phe Met Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val	
395 400 405	
AAC CTG ATC CTG GCC GTG GTC GCA ATG GCC TAT GAG GAG CAA AAC	1260
Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn	
410 415 420	
CAA GCC ACC ATC GCT GAG ACC GAG GAG AAG GAA AAG CGC TTC CAG	1305
Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Arg Phe Gln	
425 430 435	
GAG GCC ATG GAA ATG CTC AAG AAA GAA CAC GAG GCC CTC ACC ATC	1350
Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu Thr Ile	
440 445 450	
AGG GGT GTG GAT ACC GTG TCC CGT AGC TCC TTG GAG ATG TCC CCT	1395
Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser Pro	
455 460 465	
TTG GCC CCA GTA AAC AGC CAT GAG AGA AGA AGC AAG AGG AGA AAA	1440
Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys	
470 475 480	
CGG ATG TCT TCA GGA ACT GAG GAG TGT GGG GAG GAC AGG CTC CCC	1485
Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro	
485 490 495	
AAG TCT GAC TCA GAA GAT GGT CCC AGA GCA ATG AAT CAT CTC AGC	1520
Lys Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser	
500 505 510	
CTC ACC CGT GGC CTC AGC AGG ACT TCT ATG AAG CCA CGT TCC AGC	1565
Leu Thr Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser	
515 520 525	
CGC GGG AGC ATT TTC ACC TTT CGC AGG CGA GAC CTG GGT TCT GAA	1620
Arg Gly Ser Ile Phe Thr Phe Arg Arg Asp Leu Gly Ser Glu	
530 535 540	
GCA GAT TTT GCA GAT GAT GAA AAC AGC ACA GCG CGG GAG AGC GAG	1665
Ala Asp Phe Ala Asp Asp Glu Asn Ser Thr Ala Arg Glu Ser Glu	
545 550 555	
AGC CAC CAC ACA TCA CTG CTG GTG CCC TGG CCC CTG CGC CGG ACC	1710
Ser His His Thr Ser Leu Leu Val Pro Trp Pro Leu Arg Arg Thr	
560 565 570	

- 36 -

AGT	GCC	CAG	GGA	CAG	CCC	AGT	CCC	GGA	ACC	TCG	GCT	CCT	GGC	CAC	1755
Ser	Ala	Gln	Gly	Gln	Pro	Ser	Pro	Gly	Thr	Ser	Ala	Pro	Gly	His	
					575				580					585	
GCC	CTC	CAT	GGC	AAA	AAG	AAC	AGC	ACT	GTG	GAC	TGC	AAT	GGG	GTG	1800
Ala	Leu	His	Gly	Lys	Lys	Asn	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	
				590					595					600	
GTC	TCA	TTA	CTG	GGG	GCA	GGC	GAC	CCA	GAG	GCC	ACA	TCC	CCA	GGA	1845
Val	Ser	Leu	Leu	Gly	Ala	Gly	Asp	Pro	Glu	Ala	Thr	Ser	Pro	Gly	
				605					610					615	
AGC	CAC	CTC	CTC	CGC	CCT	GTG	ATG	CTA	GAG	CAC	CCG	CCA	GAC	ACG	1890
Ser	His	Leu	Leu	Arg	Pro	Val	Met	Leu	Glu	His	Pro	Pro	Asp	Thr	
				620					625					630	
ACC	ACG	CCA	TCG	GAG	GAG	CCA	GGC	GGC	CCC	CAG	ATG	CTG	ACC	TCC	1935
Thr	Thr	Pro	Ser	Glu	Glu	Pro	Gly	Gly	Pro	Gln	Met	Leu	Thr	Ser	
				635					640					645	
CAG	GCT	CCG	TGT	GTA	GAT	GGC	TTC	GAG	GAG	CCA	GGA	GCA	CGG	CAG	1980
Gln	Ala	Pro	Cys	Val	Asp	Gly	Phe	Glu	Glu	Pro	Gly	Ala	Arg	Gln	
				650					655					660	
CGG	GCC	CTC	AGC	GCA	GTC	AGC	GTC	CTC	ACA	AGC	GCA	CTG	GAA	GAG	2025
Arg	Ala	Leu	Ser	Ala	Val	Ser	Val	Leu	Thr	Ser	Ala	Leu	Glu	Glu	
				665					670					675	
TTA	GAG	GAG	TCT	CGC	CAC	AAG	TGT	CCA	CCA	TGC	TGG	AAC	CGT	CTC	2070
Leu	Glu	Glu	Ser	Arg	His	Lys	Cys	Pro	Pro	Cys	Trp	Asn	Arg	Leu	
				680					685					690	
GCC	CAG	CGC	TAC	CTG	ATC	TGG	GAG	TGC	TGC	CCG	CTG	TGG	ATG	TCC	2115
Ala	Gln	Arg	Tyr	Leu	Ile	Trp	Glu	Cys	Cys	Pro	Leu	Trp	Met	Ser	
				695					700					705	
ATC	AAG	CAG	GGA	GTG	AAG	TTG	GTG	GTC	ATG	GAC	CCG	TTT	ACT	GAC	2160
Ile	Lys	Gln	Gly	Val	Lys	Leu	Val	Val	Met	Asp	Pro	Phe	Thr	Asp	
				710					715					720	
CTC	ACC	ATC	ACT	ATG	TGC	ATC	GTA	CTC	AAC	ACA	CTC	TTC	ATG	GCG	2205
Leu	Thr	Ile	Thr	Met	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe	Met	Ala	
				725					730					735	
CTG	GAG	CAC	TAC	AAC	ATG	ACA	AGT	GAA	TTC	GAG	GAG	ATG	CTG	CAG	2250
Leu	Glu	His	Tyr	Asn	Met	Thr	Ser	Glu	Phe	Glu	Glu	Met	Leu	Gln	
				740					745					750	
GTC	GGA	AAC	CTG	GTC	TTC	ACA	GGG	ATT	TTC	ACA	GCA	GAG	ATG	ACC	2295
Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Thr	
				755					760					765	
TTC	AAG	ATC	ATT	GCC	CTC	GAC	CCC	TAC	TAC	TAC	TTC	CAA	CAG	GGC	2340
Phe	Lys	Ile	Ile	Ala	Leu	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Gln	Gly	
				770					775					780	
TGG	AAC	ATC	TTC	GAC	AGC	ATC	ATC	GTC	ATC	CTT	AGC	CTC	ATG	GAG	2385
Trp	Asn	Ile	Phe	Asp	Ser	Ile	Ile	Val	Ile	Leu	Ser	Leu	Met	Glu	
				785					790					795	
CTG	GGC	CTG	TCC	CGC	ATG	AGC	AAC	TTG	TCG	GTG	CTG	CGC	TCC	TTC	2430
Leu	Gly	Leu	Ser	Arg	Met	Ser	Asn	Leu	Ser	Val	Leu	Arg	Ser	Phe	
				800					805					810	
CGC	CTG	CTG	CGG	GTC	TTC	AAG	CTG	GCC	AAA	TCA	TGG	CCC	ACC	CTG	2475
Arg	Leu	Leu	Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	
				815					820					825	

- 37 -

AAC ACA CTC ATC AAG ATC ATC GGG AAC TCA GTG GGG GCA CTG GGG	2520
Asn Thr Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly	
830	835
	840
AAC CTG ACA CTG GTG CTA GCC ATC ATC GTG TTC ATC TTT GCT GTG	2565
Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala Val	
845	850
	855
GTG GGC ATG CAG CTC TTT GGC AAG AAC TAC TCG GAG CTG AGG GAC	2610
Val Gly Met Gln Leu Phe Gly Lys Asn Tyr Ser Glu Leu Arg Asp	
860	865
	870
AGC GAC TCA GGC CTG CTG CCT CGC TGG CAC ATG ATG GAC TTC TTT	2655
Ser Asp Ser Gly Leu Leu Pro Arg Trp His Met Met Asp Phe Phe	
875	880
	885
CAT GCC TTC CTA ATC ATC TTC CGC ATC CTC TGT GGA GAG TGG ATC	2700
His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys Gly Glu Trp Ile	
890	895
	900
GAG ACC ATG TGG GAC TGC ATG GAG GTG TCG GGG CAG TCA TTA TGC	2745
Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln Ser Leu Cys	
905	910
	915
CTG CTG GTC TTC TTG CTT GTT ATG GTC ATT GGC AAC CTT GTG GTC	2790
Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu Val Val	
920	925
	930
CTG AAT CTC TTC CTG GCC TTG CTC AGC TCC TTC AGT GCA GAC	2835
Leu Asn Leu Phe Leu Ala Leu Leu Ser Ser Phe Ser Ala Asp	
935	940
	945
AAC CTC ACA GCC CCT GAT GAG GAC AGA GAG ATG AAC AAC CTC CAG	2880
Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln	
950	955
	960
CTG GCC CTG GCC CGC ATC CAG AGG GGC CTG CGC TTT GTC AAG CGG	2925
Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg	
965	970
	975
ACC ACC TGG GAT TTC TGC TGT GGT CTC CTG CGG CAC CGG CCT CAG	2970
Thr Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg His Arg Pro Gln	
980	985
	990
AAG CCC GCA GCC CTT GCC GCC CAG GGC CAG CTG CCC AGC TGC ATT	3015
Lys Pro Ala Ala Leu Ala Gln Gly Gln Leu Pro Ser Cys Ile	
995	1000
	1005
GCC ACC CCC TAC TCC CCG CCA CCC CCA GAG ACG GAG AAG GTG CCT	3060
Ala Thr Pro Tyr Ser Pro Pro Pro Glu Thr Glu Lys Val Pro	
1010	1015
	1020
CCC ACC CGC AAG GAA ACA CAG TTT GAG GAA GGC GAG CAA CCA GGC	3105
Pro Thr Arg Lys Glu Thr Gln Phe Glu Glu Gly Glu Gln Pro Gly	
1025	1030
	1035
CAG GGC ACC CCC GGG GAT CCA GAC GCC GTG TGT GTG CCC ATC GCT	3150
Gln Gly Thr Pro Gly Asp Pro Glu Pro Val Cys Val Pro Ile Ala	
1040	1045
	1050
GTG GCC GAG TCA GAC ACA GAT GAC CAA GAA GAG GAT GAG GAG AAC	3195
Val Ala Glu Ser Asp Thr Asp Asp Gln Glu Glu Asp Glu Glu Asn	
1055	1060
	1065
AGC CTG GGC ACG GAG GAG GAG TCC AGC AAG CAG CAG GAA TCC CAG	3240
Ser Leu Gly Thr Glu Glu Glu Ser Ser Lys Gln Gln Glu Ser Gln	
1070	1075
	1080

- 38 -

CCT	GTG	TCC	GGC	TGG	CCC	AGA	GGC	CCT	CCG	GAT	TCC	AGG	ACC	TGG	3285
Pro	Val	Ser	Gly	Trp	Pro	Arg	Gly	Pro	Pro	Asp	Ser	Arg	Thr	Trp	
				1085				1090				1095			
AGC	CAG	GTG	TCA	GGC	ACT	GCC	TCC	TCT	GAG	GCC	GAG	GCC	AGT	GCA	3330
Ser	Gln	Val	Ser	Ala	Thr	Ala	Ser	Ser	Glu	Ala	Glu	Ala	Ser	Ala	
				1100				1105				1110			
TCT	CAG	GCC	GAC	TGG	CGG	CAG	CAG	TGG	AAA	GCG	GAA	CCC	CAG	GCC	3375
Ser	Gln	Ala	Asp	Trp	Arg	Gln	Gln	Trp	Lys	Ala	Glu	Pro	Gln	Ala	
				1115				1120				1125			
CCA	GGG	TGC	GGT	GAG	ACC	CCA	GAG	GAC	AGT	TGC	TCC	GAG	GGC	AGC	3420
Pro	Gly	Cys	Gly	Glu	Thr	Pro	Glu	Asp	Ser	Cys	Ser	Glu	Gly	Ser	
				1130				1135				1140			
ACA	GCA	GAC	ATG	ACC	AAC	ACC	GCT	GAG	CTC	CTG	GAG	CAG	ATC	CCT	3465
Thr	Ala	Asp	Met	Thr	Asn	Thr	Ala	Glu	Leu	Leu	Glu	Gln	Ile	Pro	
				1145				1150				1155			
GAC	CTC	GGC	CAG	GAT	GTC	AAG	GAC	CCA	GAG	GAC	TGC	TTC	ACT	GAA	3510
Asp	Leu	Gly	Gln	Asp	Val	Lys	Asp	Pro	Glu	Asp	Cys	Phe	Thr	Glu	
				1160				1165				1170			
GGC	TGT	GTC	CGG	CGC	TGT	CCC	TGC	TGT	GCG	GTG	GAC	ACC	ACA	CAG	3555
Gly	Cys	Val	Arg	Arg	Cys	Pro	Cys	Cys	Ala	Val	Asp	Thr	Thr	Gln	
				1175				1180				1185			
GCC	CCA	GGG	AAG	GTC	TGG	TGG	CGG	TTG	CGC	AAG	ACC	TGC	TAC	CAC	3600
Ala	Pro	Gly	Lys	Val	Trp	Trp	Arg	Leu	Arg	Lys	Thr	Cys	Tyr	His	
				1190				1195				1200			
ATC	GTG	GAG	CAC	AGC	TGG	TTC	GAG	ACA	TTC	ATC	ATC	TTC	ATG	ATC	3645
Ile	Val	Glu	His	Ser	Trp	Phe	Glu	Thr	Phe	Ile	Ile	Phe	Met	Ile	
				1205				1210				1215			
CTA	CTC	AGC	AGT	GGA	GCG	CTG	GCC	TTC	GAG	GAC	ATC	TAC	CTA	GAG	3690
Leu	Leu	Ser	Ser	Gly	Ala	Leu	Ala	Phe	Glu	Asp	Ile	Tyr	Leu	Glu	
				1220				1225				1230			
GAG	CGG	AAG	ACC	ATC	AAG	GTT	CTG	CTT	GAG	TAT	GCC	GAC	AAG	ATG	3735
Glu	Arg	Lys	Thr	Ile	Lys	Val	Leu	Leu	Glu	Tyr	Ala	Asp	Lys	Met	
				1235				1240				1245			
TTC	ACA	TAT	GTC	TTC	GTG	CTG	GAG	ATG	CTG	CTC	AAG	TGG	GTG	GCC	3780
Phe	Thr	Tyr	Val	Phe	Val	Leu	Glu	Met	Leu	Leu	Lys	Trp	Val	Ala	
				1250				1255				1260			
TAC	GGC	TTC	AAG	AAG	TAC	TTC	ACC	AAT	GCC	TGG	TGC	TGG	CTC	GAC	3825
Tyr	Gly	Phe	Lys	Lys	Tyr	Phe	Thr	Asn	Ala	Trp	Cys	Trp	Leu	Asp	
				1265				1270				1275			
TTC	CTC	ATC	GTA	GAC	GTC	TCT	CTG	GTC	AGC	CTG	GTG	GCC	AAC	ACC	3870
Phe	Leu	Ile	Val	Asp	Val	Ser	Leu	Val	Ser	Leu	Val	Ala	Asn	Thr	
				1280				1285				1290			
CTG	GGC	TTT	GCC	GAG	ATG	GGC	CCC	ATC	AAG	TCA	CTG	CGG	ACG	CTG	3915
Leu	Gly	Phe	Ala	Glu	Met	Gly	Pro	Ile	Lys	Ser	Leu	Arg	Thr	Leu	
				1295				1300				1305			
CGT	GCA	CTC	CGT	CCT	CTG	AGA	GCT	CTG	TCA	CGA	TTT	GAG	GGC	ATG	3960
Arg	Ala	Leu	Arg	Pro	Leu	Arg	Ala	Leu	Ser	Arg	Phe	Glu	Gly	Met	
				1310				1315				1320			
AGG	GTG	GTG	GTC	AAT	GCC	CTG	GTG	GGC	GCC	ATC	CCG	TCC	ATC	ATG	4005
Arg	Val	Val	Val	Asn	Ala	Leu	Val	Gly	Ala	Ile	Pro	Ser	Ile	Met	
				1325				1330				1335			

- 39 -

AAC GTC CTC CTC GTC CTC ATC TTC TGG CTC ATC TTC AGC ATC	4050
Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile	
1340 1345 1350	
ATG GGC GTG AAC CTC TTT GCG GGG AAG TTT GGG AGG TGC ATC AAC	4095
Met Gly Val Asn Leu Phe Ala Gly Lys Phe Gly Arg Cys Ile Asn	
1355 1360 1365	
CAG ACA GAG GGA GAC TTG CCT TTG AAC TAC ACC ATC GTG AAC AAC	4140
Gln Thr Glu Gly Asp Leu Pro Leu Asn Tyr Thr Ile Val Asn Asn	
1370 1375 1380	
AAG AGC CAG TGT GAG TCC TTG AAC TTG ACC GGA GAA TTG TAC TGG	4185
Lys Ser Gln Cys Glu Ser Leu Asn Leu Thr Gly Glu Leu Tyr Trp	
1385 1390 1395	
ACC AAG GTG AAA GTC AAC TTT GAC AAC GTG GGG GCC GGG TAC CTG	4230
Thr Lys Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu	
1400 1405 1410	
GCC CTT CTG CAG GTG GCA ACA TTT AAA GGC TGG ATG GAC ATT ATG	4275
Ala Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met	
1415 1420 1425	
TAT GCA GCT GTG GAC TCC AGG GGG TAT GAA GAG CAG CCT CAG TGG	4320
Tyr Ala Ala Val Asp Ser Arg Gly Tyr Glu Glu Gln Pro Gln Trp	
1430 1435 1440	
GAA TAC AAC CTC TAC ATG TAC ATC TAT TTT GTC ATT TTC ATC ATC	4365
Glu Tyr Asn Leu Tyr Met Tyr Ile Tyr Phe Val Ile Phe Ile Ile	
1445 1450 1455	
TTT GGG TCT TTC ACC CTG AAC CTC TTT ATT GGT GTC ATC ATT	4410
Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile	
1460 1465 1470	
GAC AAC TTC AAC CAA CAG AAG AAA AAG TTA GGG GGC CAG GAC ATC	4455
Asp Asn Phe Asn Gln Gln Lys Lys Leu Gly Gly Gln Asp Ile	
1475 1480 1485	
TTC ATG ACA GAG GAG CAG AAG TAC TAC AAT GCC ATG AAG AAG	4500
Phe Met Thr Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys	
1490 1495 1500	
CTG GGC TCC AAG AAG CCC CAG AAG CCC ATC CCA CGG CCC CTG AAC	4545
Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Leu Asn	
1505 1510 1515	
AAG TAC CAG GGC TTC ATA TTC GAC ATT GTG ACC AAG CAG GCC TTT	4590
Lys Tyr Gln Gly Phe Ile Phe Asp Ile Val Thr Lys Gln Ala Phe	
1520 1525 1530	
GAC GTC ACC ATC ATG TTT CTG ATC TGC TTG AAT ATG GTG ACC ATG	4635
Asp Val Thr Ile Met Phe Leu Ile Cys Leu Asn Met Val Thr Met	
1535 1540 1545	
ATG GTG GAG ACA GAT GAC CAA AGT CCT GAG AAA ATC AAC ATC TTG	4680
Met Val Glu Thr Asp Asp Gln Ser Pro Glu Lys Ile Asn Ile Leu	
1550 1555 1560	
GCC AAG ATC AAC CTG CTC TTT GTG GCC ATC TTC ACA GGC GAG TGT	4725
Ala Lys Ile Asn Leu Leu Phe Val Ala Ile Phe Thr Gly Glu Cys	
1565 1570 1575	
ATT GTC AAG CTG GCT GCC CTG CGC CAC TAC TAC TTC ACC AAC AGC	4770
Ile Val Lys Leu Ala Ala Leu Arg His Tyr Tyr Phe Thr Asn Ser	
1580 1585 1590	

- 40 -

TGG AAT ATC TTC GAC TTC GTG GTT GTC ATC CTC TCC ATC GTG GGC 4815  
 Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile Val Gly  
 1595 1600 1605

ACT GTG CTC TCG GAC ATC ATC CAG AAG TAC TTC TTC TCC CCG ACG 4860  
 Thr Val Leu Ser Asp Ile Ile Gln Lys Tyr Phe Phe Ser Pro Thr  
 1610 1615 1620

CTC TTC CGA GTC ATC CGC CTG GCC CGA ATA GGC CGC ATC CTC AGA 4905  
 Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg  
 1625 1630 1635

CTG ATC CGA GGG GCC AAG GGG ATC CGC ACG CTG CTC TTT GCC CTC 4950  
 Leu Ile Arg Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu  
 1640 1645 1650

ATG ATG TCC CTG CCT GCC CTC TTC AAC ATC GGG CTG CTG CTC TTC 4995  
 Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe  
 1655 1660 1665

CTC GTC ATG TTC ATC TAC TCC ATC TTT GGC ATG GCC AAC TTC GCT 5040  
 Leu Val Met Phe Ile Tyr Ser Ile Phe Gly Met Ala Asn Phe Ala  
 1670 1675 1680

TAT GTC AAG TGG GAG GCT GGC ATC GAC GAC ATG TTC AAC TTC CAG 5085  
 Tyr Val Lys Trp Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Gln  
 1685 1690 1695

ACC TTC GCC AAC AGC ATG CTG TGC CTC TTC CAG ATC ACC ACG TCG 5130  
 Thr Phe Ala Asn Ser Met Leu Cys Leu Phe Gln Ile Thr Thr Ser  
 1700 1705 1710

GCC GGC TGG GAT GGC CTC CTC AGC CCC ATC CTC AAC ACT GGG CCG 5175  
 Ala Gly Trp Asp Gly Leu Leu Ser Pro Ile Leu Asn Thr Gly Pro  
 1715 1720 1725

CCC TAC TGC GAC CCC ACT CTG CCC AAC AGC AAT GGC TCT CGG GGG 5220  
 Pro Tyr Cys Asp Pro Thr Leu Pro Asn Ser Asn Gly Ser Arg Gly  
 1730 1735 1740

GAC TGC GGG AGC CCA GCC GTG GGC ATC CTC TTC TTC ACC ACC TAC 5265  
 Asp Cys Gly Ser Pro Ala Val Gly Ile Leu Phe Phe Thr Thr Tyr  
 1745 1750 1755

ATC ATC ATC TCC TTC CTC ATC GTG GTC AAC ATG TAC ATT GCC ATC 5310  
 Ile Ile Ile Ser Phe Leu Ile Val Val Asn Met Tyr Ile Ala Ile  
 1760 1765 1770

ATC CTG GAG AAC TTC AGC GTG GCC ACG GAG GAG AGC ACC GAG CCC 5355  
 Ile Leu Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Thr Glu Pro  
 1775 1780 1785

CTG AGT GAG GAC GAC TTC GAT ATG TTC TAT GAG ATC TGG GAG AAA 5400  
 Leu Ser Glu Asp Asp Phe Asp Met Phe Tyr Glu Ile Trp Glu Lys  
 1790 1795 1800

TTT GAC CCA GAG GCC ACT CAG TTT ATT GAG TAT TCG GTC CTG TCT 5445  
 Phe Asp Pro Glu Ala Thr Gln Phe Ile Glu Tyr Ser Val Leu Ser  
 1805 1810 1815

GAC TTT GCC GAC GCC CTG TCT GAG CCA CTC CGT ATC GCC AAG CCC 5490  
 Asp Phe Ala Asp Ala Leu Ser Glu Pro Leu Ile Arg Ala Lys Pro  
 1820 1825 1830

AAC CAG ATA AGC CTC ATC AAC ATG GAC CTG CCC ATG GTG AGT GGG 5535  
 Asn Gln Ile Ser Leu Ile Asn Met Asp Leu Pro Met Val Ser Gly  
 1835 1840 1845

- 41 -

GAC CGC ATC CAT TGC ATG GAC ATT CTC TTT GCC TTC ACC AAA AGG	5580
Asp Arg Ile His Cys Met Asp Ile Leu Phe Ala Phe Thr Lys Arg	
1850	1855
	1860
GTC CTG GGG GAG TCT GGG GAG ATG GAC GCC CTG AAG ATC CAG ATG	5625
Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Lys Ile Gln Met	
1865	1870
	1875
GAG GAG AAG TTC ATG GCA GCC AAC CCA TCC AAG ATC TCC TAC GAG	5670
Glu Glu Lys Phe Met Ala Ala Asn Pro Ser Lys Ile Ser Tyr Glu	
1880	1885
	1890
CCC ATC ACC ACC ACA CTC CGG CGC AAG CAC GAA GAG GTG TCG GCC	5715
Pro Ile Thr Thr Thr Leu Arg Arg Lys His Glu Glu Val Ser Ala	
1895	1900
	1905
ATG GTT ATC CAG AGA GCC TTC CGC AGG CAC CTG CTG CAA CGC TCT	5760
Met Val Ile Gln Arg Ala Phe Arg Arg His Leu Leu Gln Arg Ser	
1910	1915
	1920
TTG AAG CAT GCC TCC TTC CTC TTC CGT CAG CAG GCG GGC AGC GGC	5805
Leu Lys His Ala Ser Phe Leu Phe Arg Gln Gln Ala Gly Ser Gly	
1925	1930
	1935
CTC TCC GAA GAG GAT GCC CCT GAG CGA GAG GGC CTC ATC GCC TAC	5850
Leu Ser Glu Glu Asp Ala Pro Glu Arg Glu Gly Leu Ile Ala Tyr	
1940	1945
	1950
GTG ATG AGT GAG AAC TTC TCC CGA CCC CTT GGC CCA CCC TCC AGC	5895
Val Met Ser Glu Asn Phe Ser Arg Pro Leu Gly Pro Pro Ser Ser	
1955	1960
	1965
TCC TCC ATC TCC TCC ACT TCC TTC CCA CCC TCC TAT GAC AGT GTC	5940
Ser Ser Ile Ser Ser Thr Ser Phe Pro Pro Ser Tyr Asp Ser Val	
1970	1975
	1980
ACT AGA GCC ACC AGC GAT AAC CTC CAG GTG CGG GGG TCT GAC TAC	5985
Thr Arg Ala Thr Ser Asp Asn Leu Gln Val Arg Gly Ser Asp Tyr	
1985	1990
	1995
AGC CAC AGT GAA GAT CTC GCC GAC TTC CCC CCT TCT CCG GAC AGG	6030
Ser His Ser Glu Asp Leu Ala Asp Phe Pro Pro Ser Pro Asp Arg	
2000	2005
	2010
GAC CGT GAG TCC ATC GTG	6048
Asp Arg Glu Ser Ile Val	
2015	

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2016 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met	Ala	Asn	Phe	Leu	Leu	Pro	Arg	Gly	Thr	Ser	Ser	Phe	Arg	Arg
1				5					10					15
Phe	Thr	Arg	Glu	Ser	Leu	Ala	Ala	Ile	Glu	Lys	Arg	Met	Ala	Glu
				20					25					30
Lys	Gln	Ala	Arg	Gly	Ser	Thr	Thr	Leu	Gln	Glu	Ser	Arg	Glu	Gly
				35					40					45
Leu	Pro	Glu	Glu	Glu	Ala	Pro	Arg	Pro	Gln	Leu	Asp	Leu	Gln	Ala
					50				55					60

- 42 -

Ser Lys Lys Leu Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu  
 65 70 75  
 Ile Gly Glu Pro Leu Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln  
 80 85 90  
 Lys Thr Phe Ile Val Leu Asn Lys Gly Lys Thr Ile Phe Arg Phe  
 95 100 105  
 Ser Ala Thr Asn Ala Leu Tyr Val Leu Ser Pro Phe His Pro Val  
 110 115 120  
 Arg Arg Ala Ala Val Lys Ile Leu Val His Ser Leu Phe Asn Met  
 125 130 135  
 Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe Met Ala Gln  
 140 145 150  
 His Asp Pro Pro Pro Trp Thr Lys Tyr Val Glu Tyr Thr Phe Thr  
 155 160 165  
 Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile Leu Ala Arg Ala  
 170 175 180  
 Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp  
 185 190 195  
 Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Glu Phe Val  
 200 205 210  
 Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg  
 215 220 225  
 Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val  
 230 235 240  
 Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val  
 245 250 255  
 Leu Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln  
 260 265 270  
 Leu Phe Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr  
 275 280 285  
 Ala Leu Asn Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val  
 290 295 300  
 Trp Glu Ser Leu Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu  
 305 310 315  
 Leu Lys Asn Gly Thr Ser Asp Val Leu Leu Cys Gly Asn Ser Ser  
 320 325 330  
 Asp Ala Gly Thr Cys Pro Glu Gly Tyr Arg Cys Leu Lys Ala Gly  
 335 340 345  
 Glu Asn Pro Asp His Gly Tyr Thr Ser Phe Asp Ser Phe Ala Trp  
 350 355 360  
 Ala Phe Leu Ala Leu Phe Arg Leu Met Thr Gln Asp Cys Trp Glu  
 365 370 375  
 Arg Leu Tyr Gln Gln Thr Leu Arg Ser Ala Gly Lys Ile Tyr Met  
 380 385 390

- 43 -

Ile Phe Phe Met Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val  
 395 400 405  
 Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn  
 410 415 420  
 Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys Arg Phe Gln  
 425 430 435  
 Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu Thr Ile  
 440 445 450  
 Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser Pro  
 455 460 465  
 Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys  
 470 475 480  
 Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro  
 485 490 495  
 Lys Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser  
 500 505 510  
 Leu Thr Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser  
 515 520 525  
 Arg Gly Ser Ile Phe Thr Phe Arg Arg Asp Leu Gly Ser Glu  
 530 535 540  
 Ala Asp Phe Ala Asp Asp Glu Asn Ser Thr Ala Arg Glu Ser Glu  
 545 550 555  
 Ser His His Thr Ser Leu Leu Val Pro Trp Pro Leu Arg Arg Thr  
 560 565 570  
 Ser Ala Gln Gly Gln Pro Ser Pro Gly Thr Ser Ala Pro Gly His  
 575 580 585  
 Ala Leu His Gly Lys Lys Asn Ser Thr Val Asp Cys Asn Gly Val  
 590 595 600  
 Val Ser Leu Leu Gly Ala Gly Asp Pro Glu Ala Thr Ser Pro Gly  
 605 610 615  
 Ser His Leu Leu Arg Pro Val Met Leu Glu His Pro Pro Asp Thr  
 620 625 630  
 Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro Gln Met Leu Thr Ser  
 635 640 645  
 Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro Gly Ala Arg Gln  
 650 655 660  
 Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala Leu Glu Glu  
 665 670 675  
 Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn Arg Leu  
 680 685 690  
 Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met Ser  
 695 700 705  
 Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp  
 710 715 720

- 44 -

Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala  
 725 730 735  
 Leu Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln  
 740 745 750  
 Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr  
 755 760 765  
 Phe Lys Ile Ile Ala Leu Asp Pro Tyr Tyr Phe Gln Gln Gly  
 770 775 780  
 Trp Asn Ile Phe Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu  
 785 790 795  
 Leu Gly Leu Ser Arg Met Ser Asn Leu Ser Val Leu Arg Ser Phe  
 800 805 810  
 Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu  
 815 820 825  
 Asn Thr Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly  
 830 835 840  
 Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala Val  
 845 850 855  
 Val Gly Met Gln Leu Phe Gly Lys Asn Tyr Ser Glu Leu Arg Asp  
 860 865 870  
 Ser Asp Ser Gly Leu Leu Pro Arg Trp His Met Met Asp Phe Phe  
 875 880 885  
 His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys Gly Glu Trp Ile  
 890 895 900  
 Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln Ser Leu Cys  
 905 910 915  
 Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu Val Val  
 920 925 930  
 Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala Asp  
 935 940 945  
 Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln  
 950 955 960  
 Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg  
 965 970 975  
 Thr Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg His Arg Pro Gln  
 980 985 990  
 Lys Pro Ala Ala Leu Ala Ala Gln Gly Gln Leu Pro Ser Cys Ile  
 995 1000 1005  
 Ala Thr Pro Tyr Ser Pro Pro Pro Glu Thr Glu Lys Val Pro  
 1010 1015 1020  
 Pro Thr Arg Lys Glu Thr Gln Phe Glu Glu Gly Glu Gln Pro Gly  
 1025 1030 1035  
 Gln Gly Thr Pro Gly Asp Pro Glu Pro Val Cys Val Pro Ile Ala  
 1040 1045 1050

- 45 -

Val Ala Glu Ser Asp Thr Asp Asp Gln Glu Glu Asp Glu Glu Asn  
 1055 1060 1065  
 Ser Leu Gly Thr Glu Glu Glu Ser Ser Lys Gln Gln Glu Ser Gln  
 1070 1075 1080  
 Pro Val Ser Gly Trp Pro Arg Gly Pro Pro Asp Ser Arg Thr Trp  
 1085 1090 1095  
 Ser Gln Val Ser Ala Thr Ala Ser Ser Glu Ala Glu Ala Ser Ala  
 1100 1105 1110  
 Ser Gln Ala Asp Trp Arg Gln Gln Trp Lys Ala Glu Pro Gln Ala  
 1115 1120 1125  
 Pro Gly Cys Gly Glu Thr Pro Glu Asp Ser Cys Ser Glu Gly Ser  
 1130 1135 1140  
 Thr Ala Asp Met Thr Asn Thr Ala Glu Leu Leu Glu Gln Ile Pro  
 1145 1150 1155  
 Asp Leu Gly Gln Asp Val Lys Asp Pro Glu Asp Cys Phe Thr Glu  
 1160 1165 1170  
 Gly Cys Val Arg Arg Cys Pro Cys Cys Ala Val Asp Thr Thr Gln  
 1175 1180 1185  
 Ala Pro Gly Lys Val Trp Trp Arg Leu Arg Lys Thr Cys Tyr His  
 1190 1195 1200  
 Ile Val Glu His Ser Trp Phe Glu Thr Phe Ile Ile Phe Met Ile  
 1205 1210 1215  
 Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Leu Glu  
 1220 1225 1230  
 Glu Arg Lys Thr Ile Lys Val Leu Leu Glu Tyr Ala Asp Lys Met  
 1235 1240 1245  
 Phe Thr Tyr Val Phe Val Leu Glu Met Leu Leu Lys Trp Val Ala  
 1250 1255 1260  
 Tyr Gly Phe Lys Lys Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp  
 1265 1270 1275  
 Phe Leu Ile Val Asp Val Ser Leu Val Ser Leu Val Ala Asn Thr  
 1280 1285 1290  
 Leu Gly Phe Ala Glu Met Gly Pro Ile Lys Ser Leu Arg Thr Leu  
 1295 1300 1305  
 Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met  
 1310 1315 1320  
 Arg Val Val Val Asn Ala Leu Val Gly Ala Ile Pro Ser Ile Met  
 1325 1330 1335  
 Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile  
 1340 1345 1350  
 Met Gly Val Asn Leu Phe Ala Gly Lys Phe Gly Arg Cys Ile Asn  
 1355 1360 1365  
 Gln Thr Glu Gly Asp Leu Pro Leu Asn Tyr Thr Ile Val Asn Asn  
 1370 1375 1380

- 46 -

Lys Ser Gln Cys Glu Ser Leu Asn Leu Thr Gly Glu Leu Tyr Trp  
 1385 1390 1395  
 Thr Lys Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu  
 1400 1405 1410  
 Ala Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met  
 1415 1420 1425  
 Tyr Ala Ala Val Asp Ser Arg Gly Tyr Glu Glu Gln Pro Gln Trp  
 1430 1435 1440  
 Glu Tyr Asn Leu Tyr Met Tyr Ile Tyr Phe Val Ile Phe Ile Ile  
 1445 1450 1455  
 Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile  
 1460 1465 1470  
 Asp Asn Phe Asn Gln Gln Lys Lys Leu Gly Gly Gln Asp Ile  
 1475 1480 1485  
 Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys  
 1490 1495 1500  
 Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Leu Asn  
 1505 1510 1515  
 Lys Tyr Gln Gly Phe Ile Phe Asp Ile Val Thr Lys Gln Ala Phe  
 1520 1525 1530  
 Asp Val Thr Ile Met Phe Leu Ile Cys Leu Asn Met Val Thr Met  
 1535 1540 1545  
 Met Val Glu Thr Asp Asp Gln Ser Pro Glu Lys Ile Asn Ile Leu  
 1550 1555 1560  
 Ala Lys Ile Asn Leu Leu Phe Val Ala Ile Phe Thr Gly Glu Cys  
 1565 1570 1575  
 Ile Val Lys Leu Ala Ala Leu Arg His Tyr Tyr Phe Thr Asn Ser  
 1580 1585 1590  
 Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile Val Gly  
 1595 1600 1605  
 Thr Val Leu Ser Asp Ile Ile Gln Lys Tyr Phe Phe Ser Pro Thr  
 1610 1615 1620  
 Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg  
 1625 1630 1635  
 Leu Ile Arg Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu  
 1640 1645 1650  
 Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe  
 1655 1660 1665  
 Leu Val Met Phe Ile Tyr Ser Ile Phe Gly Met Ala Asn Phe Ala  
 1670 1675 1680  
 Tyr Val Lys Trp Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Gln  
 1685 1690 1695  
 Thr Phe Ala Asn Ser Met Leu Cys Leu Phe Gln Ile Thr Thr Ser  
 1700 1705 1710

- 47 -

Ala Gly Trp Asp Gly Leu Leu Ser Pro Ile Leu Asn Thr Gly Pro  
 1715 1720 1725  
 Pro Tyr Cys Asp Pro Thr Leu Pro Asn Ser Asn Gly Ser Arg Gly  
 1730 1735 1740  
 Asp Cys Gly Ser Pro Ala Val Gly Ile Leu Phe Phe Thr Thr Tyr  
 1745 1750 1755  
 Ile Ile Ile Ser Phe Leu Ile Val Val Asn Met Tyr Ile Ala Ile  
 1760 1765 1770  
 Ile Leu Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Thr Glu Pro  
 1775 1780 1785  
 Leu Ser Glu Asp Asp Phe Asp Met Phe Tyr Glu Ile Trp Glu Lys  
 1790 1795 1800  
 Phe Asp Pro Glu Ala Thr Gln Phe Ile Glu Tyr Ser Val Leu Ser  
 1805 1810 1815  
 Asp Phe Ala Asp Ala Leu Ser Glu Pro Leu Ile Arg Ala Lys Pro  
 1820 1825 1830  
 Asn Gln Ile Ser Leu Ile Asn Met Asp Leu Pro Met Val Ser Gly  
 1835 1840 1845  
 Asp Arg Ile His Cys Met Asp Ile Leu Phe Ala Phe Thr Lys Arg  
 1850 1855 1860  
 Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Lys Ile Gln Met  
 1865 1870 1875  
 Glu Glu Lys Phe Met Ala Ala Asn Pro Ser Lys Ile Ser Tyr Glu  
 1880 1885 1890  
 Pro Ile Thr Thr Leu Arg Arg Lys His Glu Glu Val Ser Ala  
 1895 1900 1905  
 Met Val Ile Gln Arg Ala Phe Arg Arg His Leu Leu Gln Arg Ser  
 1910 1915 1920  
 Leu Lys His Ala Ser Phe Leu Phe Arg Gln Gln Ala Gly Ser Gly  
 1925 1930 1935  
 Leu Ser Glu Glu Asp Ala Pro Glu Arg Glu Gly Leu Ile Ala Tyr  
 1940 1945 1950  
 Val Met Ser Glu Asn Phe Ser Arg Pro Leu Gly Pro Pro Ser Ser  
 1955 1960 1965  
 Ser Ser Ile Ser Ser Thr Ser Phe Pro Pro Ser Tyr Asp Ser Val  
 1970 1975 1980  
 Thr Arg Ala Thr Ser Asp Asn Leu Gln Val Arg Gly Ser Asp Tyr  
 1985 1990 1995  
 Ser His Ser Glu Asp Leu Ala Asp Phe Pro Pro Ser Pro Asp Arg  
 2000 2005 2010  
 Asp Arg Glu Ser Ile Val  
 2015

(2) INFORMATION FOR SEQ ID NO:3:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 24 bases

- 48 -

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATGGCAAAC TCCATTAC CCGG 24

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 bases
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CACGATGGAC TCACGGTCCC TGTC 24

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3069 bases
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATG	GGG	AAG	GGG	GTT	GGA	CGT	GAT	AAG	TAT	GAG	CCT	GCA	GCT	GTT	45
Met	Gly	Lys	Gly	Val	Gly	Arg	Asp	Lys	Tyr	Glu	Pro	Ala	Ala	Val	
1				5				10						15	

TCA	GAA	CAA	GGT	GAT	AAA	AAG	GGC	AAA	AAG	GGC	AAA	AAA	GAC	AGG	90
Ser	Glu	Gln	Glu	Asp	Lys	Gly	Lys	Lys	Glu	Lys	Lys	Lys	Asp	Arg	
				20				25					30		

GAC	ATG	GAT	GAA	CTG	AAG	AAA	GAA	GTT	TCT	ATG	GAT	GAT	CAT	AAA	135
Asp	Met	Asp	Glu	Leu	Lys	Lys	Glu	Val	Ser	Met	Asp	Asp	His	Lys	
				35				40					45		

CTT	AGC	CTT	GAT	GAA	CTT	CAT	CGT	AAA	TAT	GGA	ACA	GAC	TTG	AGC	180
Leu	Ser	Leu	Asp	Glu	Leu	His	Arg	Lys	Tyr	Gly	Thr	Asp	Leu	Ser	
				50				55					60		

CGG	GGA	TTA	ACA	TCT	GCT	CGT	GCA	GCT	GAG	ATC	CTG	GCG	CGA	GAT	225
Arg	Gly	Leu	Thr	Ser	Ala	Arg	Ala	Ala	Glu	Ile	Leu	Ala	Arg	Asp	
				65				70					75		

GGT	CCC	AAC	GCC	CTC	ACT	CCC	CCT	CCC	ACT	ACT	CCT	GAA	TGG	ATC	270
Gly	Pro	Asn	Ala	Leu	Thr	Pro	Pro	Pro	Thr	Thr	Pro	Glu	Trp	Ile	
				80				85					90		

AAG	TTT	TGT	CGG	CAG	CTC	TTT	GGG	GGG	TTC	TCA	ATG	TTA	CTG	TGG	315
Lys	Phe	Cys	Arg	Gln	Leu	Phe	Gly	Gly	Phe	Ser	Met	Leu	Leu	Trp	
				95				100					105		

ATT	GGA	GCG	ATT	CTT	TGT	TTC	TTG	GCT	TAT	AGC	ATC	CAA	GCT	GCT	360
Ile	Gly	Ala	Ile	Leu	Cys	Phe	Leu	Ala	Tyr	Ser	Ile	Gln	Ala	Ala	
				110				115					120		

ACA	GAA	GAG	GAA	CCT	CAA	AAC	GAT	AAT	CTG	TAC	CTG	GGT	GTG	GTG	405
Thr	Glu	Glu	Glu	Pro	Gln	Asn	Asp	Asn	Leu	Tyr	Leu	Gly	Val	Val	
				125				130					135		

CTA	TCA	GCC	GTT	GTA	ATC	ATA	ACT	GGT	TGC	TTC	TCC	TAC	TAT	CAA	450
Leu	Ser	Ala	Val	Val	Ile	Ile	Thr	Gly	Cys	Phe	Ser	Tyr	Tyr	Gln	
				140				145					150		

- 49 -

GAA GCT AAA AGT TCA AAG ATC ATG GAA TCC TTC AAA AAC ATG GTC	495	
Glu Ala Lys Ser Ser Lys Ile Met Glu Ser Phe Lys Asn Met Val		
155	160	165
CCT CAG CAA GCC CTT GTG ATT CGA AAT GGT GAG AAA ATG AGC ATA	540	
Pro Gln Gln Ala Leu Val Ile Arg Asn Gly Glu Lys Met Ser Ile		
170	175	180
AAT GCG GAG GAA GTT GTG GTT GGG GAT CTG GTG GAA GTA AAA GGA	585	
Asn Ala Glu Glu Val Val Val Gly Asp Lue Val Glu Val Lys Gly		
185	190	195
GGA GAC CGA ATT CCT GCT GAC CTC AGA ATC ATA TCT GCA AAT GGC	630	
Gly Asp Arg Ile Pro Ala Asp Leu Arg Ile Ile Ser Ala Asn Gly		
200	205	210
TGC AAG GTG GAT AAC TCC TCG CTC ACT GGT GAA TCA GAA CCC CAG	675	
Cys Lys Val Asp Asn Ser Ser Leu Thr Gly Glu Ser Glu Pro Gln		
215	220	225
ACT AGG TCT CCA GAT TTC ACA AAT GAA AAC CCC CTG GAG ACG AGG	720	
Thr Arg Ser Pro Asp Phe Thr Asn Glu Asn Pro Leu Glu Thr Arg		
230	235	240
AAC ATT GCC TTC TTT TCA ACA AAT TGT GTT GAA GGC ACC GCA CGT	765	
Asn Ile Ala Phe Phe Ser Thr Asn Cys Val Glu Gly Thr Ala Arg		
245	250	255
GGT ATT GTT GTC TAC ACT GGG GAT CGC ACT GTG ATG GGA AGA ATT	810	
Gly Ile Val Val Tyr Thr Gly Asp Arg Thr Val Met Gly Arg Ile		
260	265	270
GCC ACA CTT GCT TCT GGG CTG GAA GGA GGC CAG ACC CCC ATT GCT	855	
Ala Thr Leu Ala Ser Gly Leu Glu Gly Gly Gln Thr Pro Ile Ala		
275	280	285
GCA GAA ATT GAA CAT TTT ATC CAC ATC ATC ACG GGT GTG GCT GTG	900	
Ala Glu Ile Glu His Phe Ile His Ile Ile Thr Gly Val Ala Val		
290	295	300
TTC CTG GGT GTG TCT TTC TTC ATC CTT TCT CTC ATC CTT GAG TAC	945	
Phe Leu Gly Val Ser Phe Phe Ile Leu Ser Leu Ile Leu Glu Tyr		
305	310	315
ACC TGG CTT GAG GCT GTC ATC TTC CTC ATC GGT ATC ATC GTA GCC	990	
Thr Trp Leu Glu Ala Val Ile Phe Leu Ile Gly Ile Ile Val Ala		
320	325	330
AAT GTG CCG GAA GGT TTG CTG GCC ACT GTC ACG GTC TGT CTG ACA	1035	
Asn Val Pro Glu Gly Leu Leu Ala Thr Val Thr Val Cys Leu Thr		
335	340	345
CTT ACT GCC AAA CGC ATG GCA AGG AAA AAC TGC TTA GTG AAG AAC	1080	
Leu Thr Ala Lys Arg Met Ala Arg Lys Asn Cys Leu Val Lys Asn		
350	355	360
TTA GAA GCT GTG GAG ACC TTG GGG TCC ACG TCC ACC ATC TGC TCT	1125	
Leu Glu Ala Val Glu Thr Leu Gly Ser Thr Ser Thr Ile Cys Ser		
365	370	375
GAT AAA ACT GGA ACT CTG ACT CAG AAC CGG ATG ACA GTG GCC CAC	1170	
Asp Lys Thr Gly Thr Leu Thr Gln Asn Arg Met Thr Val Ala His		
380	385	390
ATG TGG TTT GAC AAT CAA ATC CAT GAA GCT GAT ACG ACA GAG AAT	1215	
Met Trp Phe Asp Asn Gln Ile His Glu Ala Asp Thr Thr Glu Asn		
395	400	405

- 50 -

CAG AGT GGT GTC TCT TTT GAC AAG ACT TCA GCT ACC TGG CTT GCT 1260  
 Gln Ser Gly Val Ser Phe Asp Lys Thr Ser Ala Thr Trp Leu Ala  
 410 415 420

CTG TCC AGA ATT GCA GGT CTT TGT AAC AGG GCA GTG TTT CAG GCT 1305  
 Leu Ser Arg Ile Ala Gly Leu Cys Asn Arg Ala Val Phe Gln Ala  
 425 430 435

AAC CAG GAA AAC CTA CCT ATT CTT AAG CGG GCA GTT GCA GGA GAT 1350  
 Asn Gln Glu Asn Leu Pro Ile Leu Lys Arg Ala Val Ala Gly Asp  
 440 445 450

GCC TCT GAG TCA GCA CTC TTA AAG TGC ATA GAG CTG TGC TGT GGT 1395  
 Ala Ser Glu Ser Ala Leu Leu Lys Cys Ile Glu Leu Cys Cys Gly  
 455 460 465

TTC GTG AAG GAG ATG AGA GAA AGA TAC GCC AAA ATC GTC GAG ATA 1440  
 Ser Val Lys Glu Met Arg Glu Arg Tyr Ala Lys Ile Val Glu Ile  
 470 475 480

CCC TTC AAC TCC ACC AAC AAG TAC CAG TTG TCT ATT CAT AAG AAC 1485  
 Pro Phe Asn Ser Thr Asn Lys Tyr Gln Leu Ser Ile His Lys Asn  
 485 490 495

CCC AAC ACA TCG GAG CCC CAA CAC CTG TTG GTG ATG AAG GGC GCC 1520  
 Pro Asn Thr Ser Glu Pro Gln His Leu Leu Val Met Lys Gly Ala  
 500 505 510

CCA GAA AGG ATC CTA GAC CGT TGC AGC TCT ATC CTC CTC CAC GGC 1565  
 Pro Glu Arg Ile Leu Asp Arg Cys Ser Ser Ile Leu Leu His Gly  
 515 520 525

AAG GAG CAG CCC CTG GAT GAG GAG CTG AAA GAC GCC TTT CAG AAC 1620  
 Lys Glu Gln Pro Leu Asp Glu Glu Leu Lys Asp Ala Phe Gln Asn  
 530 535 540

GCC TAT TTG GAG CTG GGG GGC CTC GGA GAA CGA GTC CTA GGT TTC 1665  
 Ala Tyr Leu Glu Leu Gly Leu Gly Glu Arg Val Leu Gly Phe  
 545 550 555

TGC CAC CTC TTT CTG CCA GAT GAA CAG TTT CCT GAA GGG TTC CAG 1710  
 Cys His Leu Phe Leu Pro Asp Glu Gln Phe Pro Glu Gly Phe Gln  
 560 565 570

TTT GAC ACT GAC GAT GTG AAT TTC CCT ATC GAT AAT CTG TGC TTC 1755  
 Phe Asp Thr Asp Asp Val Asn Phe Pro Ile Asp Asn Leu Cys Phe  
 575 580 585

GTT GGG CTC ATC TCC ATG ATT GAC CCT CCA CGG GCG GCC GTT CCT 1800  
 Val Gly Leu Ile Ser Met Ile Asp Pro Pro Arg Ala Ala Val Pro  
 590 595 600

GAT GCC GTG GGC AAA TGT CGA AGT GCT GGA ATT AAG GTC ATC ATG 1845  
 Asp Ala Val Gly Lys Cys Arg Ser Aal Gly Ile Lys Val Ile Met  
 605 610 615

GTC ACA GGA GAC CAT CCA ATC ACA GCT AAA GCT ATT GCC AAA GGT 1890  
 Val Thr Gly Asp His Pro Ile Thr Ala Lys Ala Ile Ala Lys Gly  
 620 625 630

GTG GGC ATC ATC TCA GAA GGC ATG GAG ACC GTG GAA GAC ATT GCT 1935  
 Val Gly Ile Ile Ser Glu Gly Asn Glu Thr Val Glu Asp Ile Ala  
 635 640 645

GCC CGC CTC AAC ATC CCA GTC AGC CAG GTG AAC CCC AGG GAT GCC 1980  
 Ala Arg Leu Asn Ile Pro Val Ser Gln Val Asn Pro Arg Asp Ala  
 650 655 660

- 51 -

AAG	GCC	TGC	GTA	CAC	GGC	AGT	GAT	CTA	AAG	GAC	ATG	ACC	TCC	2025	
Lys	Ala	Cys	Val	Val	His	Gly	Ser	Asp	Leu	Lys	Asp	Met	Thr	Ser	
665									670					675	
GAG	CAG	CTG	GAT	GAC	ATT	TTG	AAG	TAC	CAC	ACT	GAG	ATA	GTG	2070	
Glu	Glm	Leu	Asp	Asp	Ile	Leu	Lys	Tyr	His	Thr	Glu	Ile	Val	Phe	
680								685						690	
GCC	AGG	ACC	TCC	CCT	CAG	CAG	AAG	CTC	ATC	ATT	GTG	GAA	GGC	2115	
Ala	Arg	Thr	Ser	Pro	Gln	Gln	Lys	Leu	Ile	Ile	Val	Glu	Gly	Cys	
695								700						705	
CAA	AGA	CAG	GGT	GCT	ATC	GTG	GCT	GTG	ACT	GGT	GAC	GGT	GTG	2160	
Gln	Arg	Gln	Gly	Ala	Ile	Val	Ala	Val	Thr	Gly	Asp	Gly	Val	Asn	
710								715						720	
GAC	TCT	CCA	GCT	TTG	AAG	AAA	GCA	GAC	ATT	GGG	GTT	GCT	ATG	2205	
Asp	Ser	Pro	Ala	Leu	Lys		Ala	Asp	Ile	Gly	Val	Ala	Met	Gly	
725								730						735	
ATT	GCT	GGC	TCA	GAT	GTG	TCC	AAG	CAA	GCT	GCT	GAC	ATG	ATT	2250	
Ile	Ala	Gly	Ser	Asp	Val	Ser	Lys	Gln	Ala	Ala	Asp	Met	Ile	Leu	
740								745						750	
CTG	GAT	GAC	AAC	TTT	GCC	TCA	ATT	GTG	ACT	GGA	GTA	GAG	GAA	2295	
Leu	Asp	Asp	Asn	Phe	Ala	Ser	Ile	Val	Thr	Gly	Val	Glu	Gly		
755								760						765	
CGT	CTG	ATC	TTT	GAT	AAC	TTG	AAG	AAA	TCC	ATT	GCT	TAT	ACC	2340	
Arg	Leu	Ile	Phe	Asp	Asn	Leu	Lys		Ser	Ile	Ala	Tyr	Thr	Leu	
770								775						780	
ACC	AGT	AAC	ATT	CCC	GAG	ATC	ACC	CCG	TTC	CTG	ATA	TTT	ATT	2385	
Thr	Ser	Asn	Ile	Pro	Glu	Ile	Thr	Pro	Phe	Leu	Ile	Phe	Ile		
785								790						795	
GCA	AAC	ATT	CCA	CTA	CCA	CTG	GGG	ACT	GTC	ACC	ATC	CTC	TGC	2430	
Ala	Asn	Ile	Pro	Leu	Pro	Leu	Gly	Thr	Val	Thr	Ile	Leu	Cys	Ile	
800								805						810	
GAC	TTG	GGC	ACT	GAC	ATG	GTT	CCT	GCC	ATC	TCC	CTG	GCT	TAT	2475	
Asp	Leu	Gly	Thr	Asp	Met	Val	Pro	Ala	Ile	Ser	Leu	Ala	Tyr	Glu	
815								820						825	
CAG	GCT	GAG	AGT	GAC	ATC	ATG	AAG	AGA	CAG	CCC	AGA	AAT	CCC	AAA	2520
Gln	Ala	Glu	Ser	Asp	Ile	Met	Lys	Arg	Gln	Pro	Arg	Asn	Pro	Lys	
830								835						840	
ACA	GAC	AAA	CTT	GTG	AAT	GAG	CGG	CTG	ATC	AGC	ATG	GCC	TAT	2565	
Thr	Asp	Lys	Leu	Val	Asn	Glu	Arg	Leu	Ile	Ser	Met	Ala	Tyr	Gly	
845								850						855	
CAG	ATT	GGA	ATG	ATC	CAG	GCC	CTG	GGA	GGC	TTC	TTT	ACT	TAC	2610	
Gln	Ile	Gly	Met	Ile	Gln	Ala	Leu	Gly	Gly	Phe	Phe	Thr	Tyr	Phe	
860								865						870	
GTG	ATT	CTG	GCT	GAG	AAC	GGC	TTC	CTC	CCA	ATT	CAC	CTG	TTG	2655	
Val	Ile	Leu	Ala	Glu	Asn	Gly	Phe	Leu	Pro	Ile	His	Leu	Leu	Gly	
875								880						885	
CTC	CGA	GTG	GAC	TGG	GAT	GAC	CGC	TGG	ATC	AAC	GAT	GTG	GAA	GAC	2700
Leu	Arg	Val	Asp	Trp	Asp	Asp	Arg	Trp	Ile	Asn	Asp	Val	Glu	Asp	
890								895						900	
AGC	TAC	GGG	CAG	CAG	TGG	ACC	TAT	GAG	CAG	AGG	AAA	ATC	GTG	GAG	2745
Ser	Tyr	Gly	Gln	Gln	Trp	Thr	Tyr	Glu	Gln	Arg	Lys	Ile	Val	Glu	
905								910						915	

- 52 -

TTC ACC TGC CAC ACA GCC TTC TTC GTC AGT ATC GTG GTG GTG CAG	2790																																																						
Phe Thr Cys His Thr Ala Phe Phe Val Ser Ile Val Val Val Gln																																																							
920	925		930	TGG GCC GAC TTG GTC ATC TGT AAG ACC AGG AGG AAT TCG GTC TTC	2835	Trp Ala Asp Leu Val Ile Cys Lys Thr Arg Arg Asn Ser Val Phe		935	940		945	CAG CAG GGG ATG AAG AAC AAG ATC TTG ATA TTT GGC CTC TTT GAA	2880	Gln Gln Gly Met Lys Asn Lys Ile Leu Ile Phe Gly Leu Phe Glu		950	955		960	GAG ACA GCC CTG GCT GCT TTC CTT TCC TAC TGC CCT GGA ATG GGT	2925	Glu Thr Ala Leu Ala Ala Phe Leu Ser Tyr Cys Pro Gly Met Gly		965	970		975	GTT GCT CTT AGG ATG TAT CCC CTC AAA CCT ACC TGG TGG TTC TGT	2970	Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys		980	985		990	GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015	Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg		995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr	
	930																																																						
TGG GCC GAC TTG GTC ATC TGT AAG ACC AGG AGG AAT TCG GTC TTC	2835																																																						
Trp Ala Asp Leu Val Ile Cys Lys Thr Arg Arg Asn Ser Val Phe																																																							
935	940		945	CAG CAG GGG ATG AAG AAC AAG ATC TTG ATA TTT GGC CTC TTT GAA	2880	Gln Gln Gly Met Lys Asn Lys Ile Leu Ile Phe Gly Leu Phe Glu		950	955		960	GAG ACA GCC CTG GCT GCT TTC CTT TCC TAC TGC CCT GGA ATG GGT	2925	Glu Thr Ala Leu Ala Ala Phe Leu Ser Tyr Cys Pro Gly Met Gly		965	970		975	GTT GCT CTT AGG ATG TAT CCC CTC AAA CCT ACC TGG TGG TTC TGT	2970	Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys		980	985		990	GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015	Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg		995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr									
	945																																																						
CAG CAG GGG ATG AAG AAC AAG ATC TTG ATA TTT GGC CTC TTT GAA	2880																																																						
Gln Gln Gly Met Lys Asn Lys Ile Leu Ile Phe Gly Leu Phe Glu																																																							
950	955		960	GAG ACA GCC CTG GCT GCT TTC CTT TCC TAC TGC CCT GGA ATG GGT	2925	Glu Thr Ala Leu Ala Ala Phe Leu Ser Tyr Cys Pro Gly Met Gly		965	970		975	GTT GCT CTT AGG ATG TAT CCC CTC AAA CCT ACC TGG TGG TTC TGT	2970	Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys		980	985		990	GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015	Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg		995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr																	
	960																																																						
GAG ACA GCC CTG GCT GCT TTC CTT TCC TAC TGC CCT GGA ATG GGT	2925																																																						
Glu Thr Ala Leu Ala Ala Phe Leu Ser Tyr Cys Pro Gly Met Gly																																																							
965	970		975	GTT GCT CTT AGG ATG TAT CCC CTC AAA CCT ACC TGG TGG TTC TGT	2970	Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys		980	985		990	GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015	Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg		995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr																									
	975																																																						
GTT GCT CTT AGG ATG TAT CCC CTC AAA CCT ACC TGG TGG TTC TGT	2970																																																						
Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys																																																							
980	985		990	GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015	Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg		995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr																																	
	990																																																						
GCC TTC CCC TAC TCT CTT CTC ATC TTC GTA TAT GAC GAA GTC AGA	3015																																																						
Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg																																																							
995	1000		1005	AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060	Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu		1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr																																									
	1005																																																						
AAA CTC ATC ATC AGG CGA CGC CCT GGC GGC TGG GTG GAG AAG GAA	3060																																																						
Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu																																																							
1010	1015		1020	ACC TAC TAT 3069		Thr Tyr Tyr																																																	
	1020																																																						
ACC TAC TAT 3069																																																							
Thr Tyr Tyr																																																							

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1023 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Lys Gly Val Gly Arg Asp Lys Tyr Glu Pro Ala Ala Val																																																					
1	5		10		15	Ser Glu Gln Glu Asp Lys Lys Glu Lys Lys Glu Lys Lys Asp Arg		20	25		30	Asp Met Asp Glu Leu Lys Lys Glu Val Ser Met Asp Asp His Lys		35	40		45	Leu Ser Leu Asp Glu Leu His Arg Lys Tyr Gly Thr Asp Leu Ser		50	55		60	Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp		65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135
	10		15	Ser Glu Gln Glu Asp Lys Lys Glu Lys Lys Glu Lys Lys Asp Arg		20	25		30	Asp Met Asp Glu Leu Lys Lys Glu Val Ser Met Asp Asp His Lys		35	40		45	Leu Ser Leu Asp Glu Leu His Arg Lys Tyr Gly Thr Asp Leu Ser		50	55		60	Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp		65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135		
	15																																																				
Ser Glu Gln Glu Asp Lys Lys Glu Lys Lys Glu Lys Lys Asp Arg																																																					
20	25		30	Asp Met Asp Glu Leu Lys Lys Glu Val Ser Met Asp Asp His Lys		35	40		45	Leu Ser Leu Asp Glu Leu His Arg Lys Tyr Gly Thr Asp Leu Ser		50	55		60	Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp		65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135								
	30																																																				
Asp Met Asp Glu Leu Lys Lys Glu Val Ser Met Asp Asp His Lys																																																					
35	40		45	Leu Ser Leu Asp Glu Leu His Arg Lys Tyr Gly Thr Asp Leu Ser		50	55		60	Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp		65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135														
	45																																																				
Leu Ser Leu Asp Glu Leu His Arg Lys Tyr Gly Thr Asp Leu Ser																																																					
50	55		60	Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp		65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135																				
	60																																																				
Arg Gly Leu Thr Ser Ala Arg Ala Ala Glu Ile Leu Ala Arg Asp																																																					
65	70		75	Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile		80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135																										
	75																																																				
Gly Pro Asn Ala Leu Thr Pro Pro Pro Thr Thr Pro Glu Trp Ile																																																					
80	85		90	Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp		95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135																																
	90																																																				
Lys Phe Cys Arg Gln Leu Phe Gly Gly Phe Ser Met Leu Leu Trp																																																					
95	100		105	Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala		110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135																																						
	105																																																				
Ile Gly Ala Ile Leu Cys Phe Leu Ala Tyr Ser Ile Gln Ala Ala																																																					
110	115		120	Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val		125	130		135																																												
	120																																																				
Thr Glu Glu Glu Pro Gln Asn Asp Asn Leu Tyr Leu Gly Val Val																																																					
125	130		135																																																		
	135																																																				

- 53 -

Leu Ser Ala Val Val Ile Ile Thr Gly Cys Phe Ser Tyr Tyr Gln  
 140 145 150  
 Glu Ala Lys Ser Ser Lys Ile Met Glu Ser Phe Lys Asn Met Val  
 155 160 165  
 Pro Gln Gln Ala Leu Val Ile Arg Asn Gly Glu Lys Met Ser Ile  
 170 175 180  
 Asn Ala Glu Glu Val Val Val Gly Asp Lue Val Glu Val Lys Gly  
 185 190 195  
 Gly Asp Arg Ile Pro Ala Asp Leu Arg Ile Ile Ser Ala Asn Gly  
 200 205 210  
 Cys Lys Val Asp Asn Ser Ser Leu Thr Gly Glu Ser Glu Pro Gln  
 215 220 225  
 Thr Arg Ser Pro Asp Phe Thr Asn Glu Asn Pro Leu Glu Thr Arg  
 230 235 240  
 Asn Ile Ala Phe Phe Ser Thr Asn Cys Val Glu Gly Thr Ala Arg  
 245 250 255  
 Gly Ile Val Val Tyr Thr Gly Asp Arg Thr Val Met Gly Arg Ile  
 260 265 270  
 Ala Thr Leu Ala Ser Gly Leu Glu Gly Gly Gln Thr Pro Ile Ala  
 275 280 285  
 Ala Glu Ile Glu His Phe Ile His Ile Ile Thr Gly Val Ala Val  
 290 295 300  
 Phe Leu Gly Val Ser Phe Phe Ile Leu Ser Leu Ile Leu Glu Tyr  
 305 310 315  
 Thr Trp Leu Glu Ala Val Ile Phe Leu Ile Gly Ile Ile Val Ala  
 320 325 330  
 Asn Val Pro Glu Gly Leu Leu Ala Thr Val Thr Val Cys Leu Thr  
 335 340 345  
 Leu Thr Ala Lys Arg Met Ala Arg Lys Asn Cys Leu Val Lys Asn  
 350 355 360  
 Leu Glu Ala Val Glu Thr Leu Gly Ser Thr Ser Thr Ile Cys Ser  
 365 370 375  
 Asp Lys Thr Gly Thr Leu Thr Gln Asn Arg Met Thr Val Ala His  
 380 385 390  
 Met Trp Phe Asp Asn Gln Ile His Glu Ala Asp Thr Thr Glu Asn  
 395 400 405  
 Gln Ser Gly Val Ser Phe Asp Lys Thr Ser Ala Thr Trp Leu Ala  
 410 415 420  
 Leu Ser Arg Ile Ala Gly Leu Cys Asn Arg Ala Val Phe Gln Ala  
 425 430 435  
 Asn Gln Glu Asn Leu Pro Ile Leu Lys Arg Ala Val Ala Gly Asp  
 440 445 450  
 Ala Ser Glu Ser Ala Leu Leu Lys Cys Ile Glu Leu Cys Cys Gly  
 455 460 465

- 54 -

Ser Val Lys Glu Met Arg Glu Arg Tyr Ala Lys Ile Val Glu Ile  
 470 475 480  
 Pro Phe Asn Ser Thr Asn Lys Tyr Gln Leu Ser Ile His Lys Asn  
 485 490 495  
 Pro Asn Thr Ser Glu Pro Gln His Leu Leu Val Met Lys Gly Ala  
 500 505 510  
 Pro Glu Arg Ile Leu Asp Arg Cys Ser Ser Ile Leu Leu His Gly  
 515 520 525  
 Lys Glu Gln Pro Leu Asp Glu Glu Leu Lys Asp Ala Phe Gln Asn  
 530 535 540  
 Ala Tyr Leu Glu Leu Gly Gly Leu Gly Glu Arg Val Leu Gly Phe  
 545 550 555  
 Cys His Leu Phe Leu Pro Asp Glu Gln Phe Pro Glu Gly Phe Gln  
 560 565 570  
 Phe Asp Thr Asp Asp Val Asn Phe Pro Ile Asp Asn Leu Cys Phe  
 575 580 585  
 Val Gly Leu Ile Ser Met Ile Asp Pro Pro Arg Ala Ala Val Pro  
 590 595 600  
 Asp Ala Val Gly Lys Cys Arg Ser Aal Gly Ile Lys Val Ile Met  
 605 610 615  
 Val Thr Gly Asp His Pro Ile Thr Ala Lys Ala Ile Ala Lys Gly  
 620 625 630  
 Val Gly Ile Ile Ser Glu Gly Asn Glu Thr Val Glu Asp Ile Ala  
 635 640 645  
 Ala Arg Leu Asn Ile Pro Val Ser Gln Val Asn Pro Arg Asp Ala  
 650 655 660  
 Lys Ala Cys Val Val His Gly Ser Asp Leu Lys Asp Met Thr Ser  
 665 670 675  
 Glu Glu Leu Asp Asp Ile Leu Lys Tyr His Thr Glu Ile Val Phe  
 680 685 690  
 Ala Arg Thr Ser Pro Gln Gln Lys Leu Ile Ile Val Glu Gly Cys  
 695 700 705  
 Gln Arg Gln Gly Ala Ile Val Ala Val Thr Gly Asp Gly Val Asn  
 710 715 720  
 Asp Ser Pro Ala Leu Lys Lys Ala Asp Ile Gly Val Ala Met Gly  
 725 730 735  
 Ile Ala Gly Ser Asp Val Ser Lys Gln Ala Ala Asp Met Ile Leu  
 740 745 750  
 Leu Asp Asp Asn Phe Ala Ser Ile Val Thr Gly Val Glu Glu Gly  
 755 760 765  
 Arg Leu Ile Phe Asp Asn Leu Lys Lys Ser Ile Ala Tyr Thr Leu  
 770 775 780  
 Thr Ser Asn Ile Pro Glu Ile Thr Pro Phe Leu Ile Phe Ile Ile  
 785 790 795

- 55 -

Ala Asn Ile Pro Leu Pro Leu Gly Thr Val Thr Ile Leu Cys Ile  
 800 805 810  
 Asp Leu Gly Thr Asp Met Val Pro Ala Ile Ser Leu Ala Tyr Glu  
 815 820 825  
 Gln Ala Glu Ser Asp Ile Met Lys Arg Gln Pro Arg Asn Pro Lys  
 830 835 840  
 Thr Asp Lys Leu Val Asn Glu Arg Leu Ile Ser Met Ala Tyr Gly  
 845 850 855  
 Gln Ile Gly Met Ile Gln Ala Leu Gly Gly Phe Phe Thr Tyr Phe  
 860 865 870  
 Val Ile Leu Ala Glu Asn Gly Phe Leu Pro Ile His Leu Leu Gly  
 875 880 885  
 Leu Arg Val Asp Trp Asp Asp Arg Trp Ile Asn Asp Val Glu Asp  
 890 895 900  
 Ser Tyr Gly Gln Gln Trp Thr Tyr Glu Gln Arg Lys Ile Val Glu  
 905 910 915  
 Phe Thr Cys His Thr Ala Phe Phe Val Ser Ile Val Val Val Gln  
 920 925 930  
 Trp Ala Asp Leu Val Ile Cys Lys Thr Arg Arg Asn Ser Val Phe  
 935 940 945  
 Gln Gln Gly Met Lys Asn Lys Ile Leu Ile Phe Gly Leu Phe Glu  
 950 955 960  
 Glu Thr Ala Leu Ala Ala Phe Leu Ser Tyr Cys Pro Gly Met Gly  
 965 970 975  
 Val Ala Leu Arg Met Tyr Pro Leu Lys Pro Thr Trp Trp Phe Cys  
 980 985 990  
 Ala Phe Pro Tyr Ser Leu Leu Ile Phe Val Tyr Asp Glu Val Arg  
 995 1000 1005  
 Lys Leu Ile Ile Arg Arg Arg Pro Gly Gly Trp Val Glu Lys Glu  
 1010 1015 1020

Thr Tyr Tyr

## (2) INFORMATION FOR SEQ ID NO:7:

## (I) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 909 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATG	GCC	CGC	GGG	AAA	GCC	AAG	GAG	GAG	GGC	AGC	TGG	AAG	AAA	TTC	45
Met	Ala	Arg	Gly	Lys	Ala	Lys	Glu	Glu	Gly	Ser	Trp	Lys	Lys	Phe	
1					5				10					15	
ATC	TGG	AAC	TCA	GAG	AAG	AAG	GAG	TTT	CTG	GGC	AGG	ACC	GGT	GGC	90
Ile	Trp	Asn	Ser	Glu	Lys	Glu	Phe	Leu	Gly	Arg	Thr	Gly	Gly		
20								25					30		
AGT	TGG	TTT	AAG	ATC	CTT	CTA	TTC	TAC	GTA	ATA	TTT	TAT	GGC	TGC	135
Ser	Trp	Phe	Lys	Ile	Leu	Leu	Phe	Tyr	Val	Ile	Phe	Tyr	Gly	Cys	
35								40					45		

- 56 -

CTG GCT GGC ATC TTC ATC GGA ACC ATC CAA GTG ATG CTG CTC ACC	180
Leu Ala Gly Ile Phe Ile Gly Thr Ile Gln Val Met Leu Leu Thr	
50 55 60	
ATC AGT GAA TTT AAG CCC ACA TAT CAG GAC CGA GTG GCC CCG CCA	225
Ile Ser Glu Phe Lys Pro Thr Tyr Gln Asp Arg Val Ala Pro Pro	
65 70 75	
GGA TTA ACA CAG ATT CCT CAG ATC CAG AAG ACT GAA ATT TCC TTT	270
Gly Leu Thr Gln Ile Pro Gln Ile Gln Lys Thr Glu Ile Ser Phe	
80 85 90	
CGT CCT AAT GAT CCC AAG AGC TAT GAG GCA TAT GTA CTG AAC ATA	315
Arg Pro Asn Asp Pro Lys Ser Tyr Glu Ala Tyr Val Leu Asn Ile	
95 100 105	
GTT AGG TTC CTG GAA AAG TAC AAA GAT TCA GCC CAG AGG GAT GAC	360
Val Arg Phe Leu Glu Lys Tyr Lys Asp Ser Ala Gln Arg Asp Asp	
110 115 120	
ATG ATT TTT GAA GAT TGT GGC GAT GTG CCC AGT GAA CCG AAA GAA	405
Met Ile Phe Glu Asp Cys Gly Asp Val Pro Ser Glu Pro Lys Glu	
125 130 135	
CGA GGA GAC TTT AAT CAT GAA CGA GGA GAG CGA AAG GTC TGC AGA	450
Arg Gly Asp Phe Asn His Glu Arg Gly Glu Arg Lys Val Cys Arg	
140 145 150	
TTC AAG CTT GAA TGG CTG GGA AAT TGC TCT GGA TTA AAT GAT GAA	495
Phy Lys Leu Glu Trp Leu Gly Asn Cys Ser Gly Leu Asn Asp Glu	
155 160 165	
ACT TAT GGC TAC AAA GAG GGC AAA CCG TGC ATT ATT ATA AAG CTC	540
Thr Tyr Gly Tyr Lys Glu Gly Lys Pro Cys Ile Ile Ile Lys Leu	
170 175 180	
AAC CGA GTT CTA GGC TTC AAA CCT AAG CCT CCC AAG AAT GAG TCC	585
Asn Arg Val Leu Gly Phe Lys Pro Lys Pro Pro Lys Asn Glu Ser	
185 190 195	
TTG GAG ACT TAC CCA GTG ATG AAG TAT AAC CCA AAT GTC CTT CCC	630
Leu Glu Thr Tyr Pro Val Met Lys Tyr Asn Pro Asn Val Leu Pro	
200 205 210	
GTT CAG TGC ACT GGC AAG CGA GAT GAA GAT AAG GAT AAA GTT GGA	675
Val Gln Cys Thr Gly Lys Arg Asp Glu Asp Lys Asp Lys Val Gly	
215 220 225	
AAT GTG GAG TAT TTT GGA CTG GGC AAC TCC CCT GGT TTT CCT CTG	720
Asn Val Glu Tyr Phe Gly Leu Gly Asn Ser Pro Gly Phe Pro Leu	
230 235 240	
CAG TAT TAT CCG TAC TAT GGC AAA CTC CTG CAG CCC AAA TAC CTG	765
Gln Tyr Tyr Pro Tyr Gly Lys Leu Leu Gln Pro Lys Tyr Leu	
245 250 255	
CAG CCC CTG CTG GCC GTA CAG TTC ACC AAT CTT ACC ATG GAC ACT	810
Gln Pro Leu Leu Ala Val Gln Phe Thr Asn Leu Thr Met Asp Thr	
260 265 270	
GAA ATT CGC ATA GAG TGT AAG GCG TAC GGT GAG AAC ATT GGG TAC	855
Glu Ile Arg Ile Glu Cys Lys Ala Tyr Gly Glu Asn Ile Gly Tyr	
275 280 285	
AGT GAG AAA GAC CGT TTT CAG GGA CGT TTT GAT GTA AAA ATT GAA	900
Ser Glu Lys Asp Arg Phe Gln Gly Arg Phe Asp Val Lys Ile Glu	
290 295 300	

GTT AAG AGC 909  
 Val Lys Ser

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 303 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ala Arg Gly Lys Ala Lys Glu Glu Gly Ser Trp Lys Lys Phe  
 1 5 10 15

Ile Trp Asn Ser Glu Lys Lys Glu Phe Leu Gly Arg Thr Gly Gly  
 20 25 30

Ser Trp Phe Lys Ile Leu Leu Phe Tyr Val Ile Phe Tyr Gly Cys  
 35 40 45

Leu Ala Gly Ile Phe Ile Gly Thr Ile Gln Val Met Leu Leu Thr  
 50 55 60

Ile Ser Glu Phe Lys Pro Thr Tyr Gln Asp Arg Val Ala Pro Pro  
 65 70 75

Gly Leu Thr Gln Ile Pro Gln Ile Gln Lys Thr Glu Ile Ser Phe  
 80 85 90

Arg Pro Asn Asp Pro Lys Ser Tyr Glu Ala Tyr Val Leu Asn Ile  
 95 100 105

Val Arg Phe Leu Glu Lys Tyr Lys Asp Ser Ala Gln Arg Asp Asp  
 110 115 120

Met Ile Phe Glu Asp Cys Gly Asp Val Pro Ser Glu Pro Lys Glu  
 125 130 135

Arg Gly Asp Phe Asn His Glu Arg Gly Glu Arg Lys Val Cys Arg  
 140 145 150

Phy Lys Leu Glu Trp Leu Gly Asn Cys Ser Gly Leu Asn Asp Glu  
 155 160 165

Thr Tyr Gly Tyr Lys Glu Gly Lys Pro Cys Ile Ile Ile Lys Leu  
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Asn Arg Val Leu Gly Phe Lys Pro Lys Pro Pro Lys Asn Glu Ser  
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Leu Glu Thr Tyr Pro Val Met Lys Tyr Asn Pro Asn Val Leu Pro  
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Val Gln Cys Thr Gly Lys Arg Asp Glu Asp Lys Asp Lys Val Gly  
 215 220 225

Asn Val Glu Tyr Phe Gly Leu Gly Asn Ser Pro Gly Phe Pro Leu  
 230 235 240

Gln Tyr Tyr Pro Tyr Tyr Gly Lys Leu Leu Gln Pro Lys Tyr Leu  
 245 250 255

Gln Pro Leu Leu Ala Val Gln Phe Thr Asn Leu Thr Met Asp Thr  
 260 265 270

- 58 -

Glu Ile Arg Ile Glu Cys Lys Ala Tyr Gly Glu Asn Ile Gly Tyr  
275 280 285

Ser Glu Lys Asp Arg Phe Gln Gly Arg Phe Asp Val Lys Ile Glu  
290 295 300

Val Lys Ser

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATGGGGAAGG GGGTTGGACG TGAT 24

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

ATAGTAGGTT TCCTTCTCCA CCCA 24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ATGGCCCGCG GGAAAGCCAA GGAG 24

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 bases
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCTCTTAACT TCAATTTTA CATC 24

## WHAT IS CLAIMED IS:

1. A delivery system for delivering a therapeutically effective amount of a predetermined genetic material to myocardial cells of a chosen location of a patient's heart, said genetic material being selected for the function of increasing the amplitude of the patient's cardiac signal so that it can be better sensed by an electrode, comprising:

10 a supply of said genetic material; reservoir means for containing said genetic material; and

15 delivery means for delivering said genetic material from said reservoir to said myocardial cells, thereby increasing the amplitude of the cardiac signal and improving the signal to noise ratio that can be sensed by a pacemaker.

2. The delivery system of claim 1, wherein said supply of genetic material comprises a bolus of ion channel 20 protein genetic material selected for the function of increasing the amplitude of the cardiac signal.

3. The delivery system of claim 1, wherein said delivery means comprises a catheter with a distal end portion, and said reservoir means is located in said distal 25 end portion.

4. The delivery system of claim 3, wherein said distal end portion comprises a hollow helical element forming an interior, and said reservoir means comprises said interior with said supply therein.

30 5. The delivery system of claim 1, wherein said delivery means comprises a catheter with a lumen for delivering said genetic material therethrough, said catheter having a distal tip communicating with said lumen for

- 60 -

contacting said plurality of cells in the proximity of said electrode with said genetic material.

6. The delivery system of claim 5, wherein said distal tip is a hollow helical needle tip.

5 7. The delivery system of claim 5, wherein said catheter is a transvenous endocardial catheter.

8. The delivery system of claim 1, wherein said reservoir contains a supply of 0.1-10 ml of said genetic material.

10 9. The delivery system of claim 1, wherein said delivery means comprises a catheter with a distal portion and an end tip, and wherein said reservoir means is contained in said distal portion, and further comprising force means for forcing said genetic material from said 15 reservoir means and out of said end tip.

10. The delivery system of claim 9, wherein said force means comprises a stylet.

11. The delivery system of claim 1, wherein said delivery system comprises a hollow helical screw-in element 20 loaded with a bolus of said genetic material.

12. The delivery system of claim 11, wherein said element comprises ports for egress of said genetic material into said identified cardiac location when said element is screwed into said location, and further comprising soluble 25 plugs in said ports to maintain them normally closed but which dissolve when said element is positioned within said patient's heart.

13. The delivery system of claim 1, wherein said predetermined genetic material is DNA or RNA, and imparts

- 61 -

chronic change in ion channel expression in said cardiac cells.

14. The delivery system of claim 1, wherein said delivery means comprises a catheter with a distal end portion, and said reservoir means is located in said distal end portion.

15. The delivery system of claim 13, wherein said DNA or RNA encodes an ion channel protein.

16. The delivery system of claim 15, wherein said ion channel protein is a sodium channel protein.

17. The delivery system of claim 16, wherein said sodium channel protein is hH1.

18. The delivery system of claim 1, wherein said predetermined genetic material is protein, and imparts acute change in sodium channel expression in said cardiac cells.

19. The delivery system of claim 18, wherein said protein is an ion channel protein.

20. The delivery system of claim 19, wherein said ion channel protein is a sodium channel protein.

21. The delivery system of claim 20, wherein said sodium channel protein is hH1.

22. An implantable delivery system for delivering doses of a therapeutically effective amount of a predetermined genetic material to myocardial cells in a chosen location of a patient's heart, comprising:

a supply of genetic material of the class having the property of increasing the expression of ion channels in the myocardial cells to which it is delivered;

- 62 -

a catheter, said catheter having a distal tip portion for engaging the cells of said chosen location and delivering thereto said genetic material;

5 reservoir means for holding said supply of genetic material and providing it to said distal tip portion of said catheter; and

10 delivery means for delivering a therapeutically effective amount of said genetic material from said reservoir means through said distal tip portion to said chosen location.

23. The system as described in claim 20, further comprising:

15 control means for controlling operation of said delivery means to deliver respective said doses.

24. The implantable delivery system of claim 23, wherein said control means comprises initiating means for initiating delivery of said genetic material, said initiating means comprising an external programmer.

20 25. The implantable delivery system of claim 23, wherein said control means comprises automatic means for automatically initiating delivery of said genetic material.

25 26. An implantable delivery system for delivering predetermined genetic material to cardiac cells adjacent to a pacing electrode positioned against the inner wall of a patient's heart, comprising:

a supply of genetic material of the class having the property of increasing the expression of ion channels in cardiac cells to which it is delivered;

30 a catheter, said catheter having a distal tip portion for engaging said cardiac cells and delivering thereto said genetic material;

reservoir means for holding said supply of genetic material and providing it to said distal tip portion of said catheter; and

5 delivery means for delivering a therapeutically effective amount of said genetic material from said reservoir means through said distal tip portion to said cardiac cells.

27. The implantable delivery system of claim 26, wherein the distal end of said distal tip portion further 10 comprises a pacing electrode.

28. The system as described in claim 26, further comprising:

control means for controlling operation of said delivery means to deliver respective said doses.

15 29. The implantable delivery system of claim 26, wherein said control means comprises initiating means for initiating delivery of said genetic material, said initiating means comprising an external programmer.

30. The implantable delivery system of claim 26, 20 wherein said control means comprises automatic means for automatically initiating delivery of said genetic material.

31. An implantable system for pacing a patient's heart and for delivering a predetermined genetic material to cardiac cells adjacent to a pacing electrode positioned in 25 said patient's heart, comprising:

a supply of genetic material of the class having the property of increasing the expression of ion channels in cardiac cells to which it is delivered;

30 a catheter, said catheter having proximal and distal ends, a lumen through at least a part thereof and connecting to said distal end, a pacing electrode positioned at said distal end for engaging said patient's heart wall,

- 64 -

said electrode having a channel therethrough in communication with said lumen, and a conductor connecting said proximal end to said electrode,

5 a pulse generator connected electrically to said conductor at said catheter proximal end for delivering pace pulses to said electrode,

reservoir means for holding said supply of genetic material, and

10 delivery means for delivering said genetic material from said reservoir to said lumen, whereby said material passes through said lumen and said channel to said heart wall.

32. The implantable system of claim 31, wherein said reservoir is mounted in said pulse generator.

15 33. The implantable system of claim 31, wherein said delivery means is passive.

34. The implantable system of claim 31, wherein said delivery means comprises a pump.

20 35. The implantable system of claim 31, wherein said electrode is substantially concentric with respect to the catheter axis, and the channel passes through the center of said electrode.

1/5

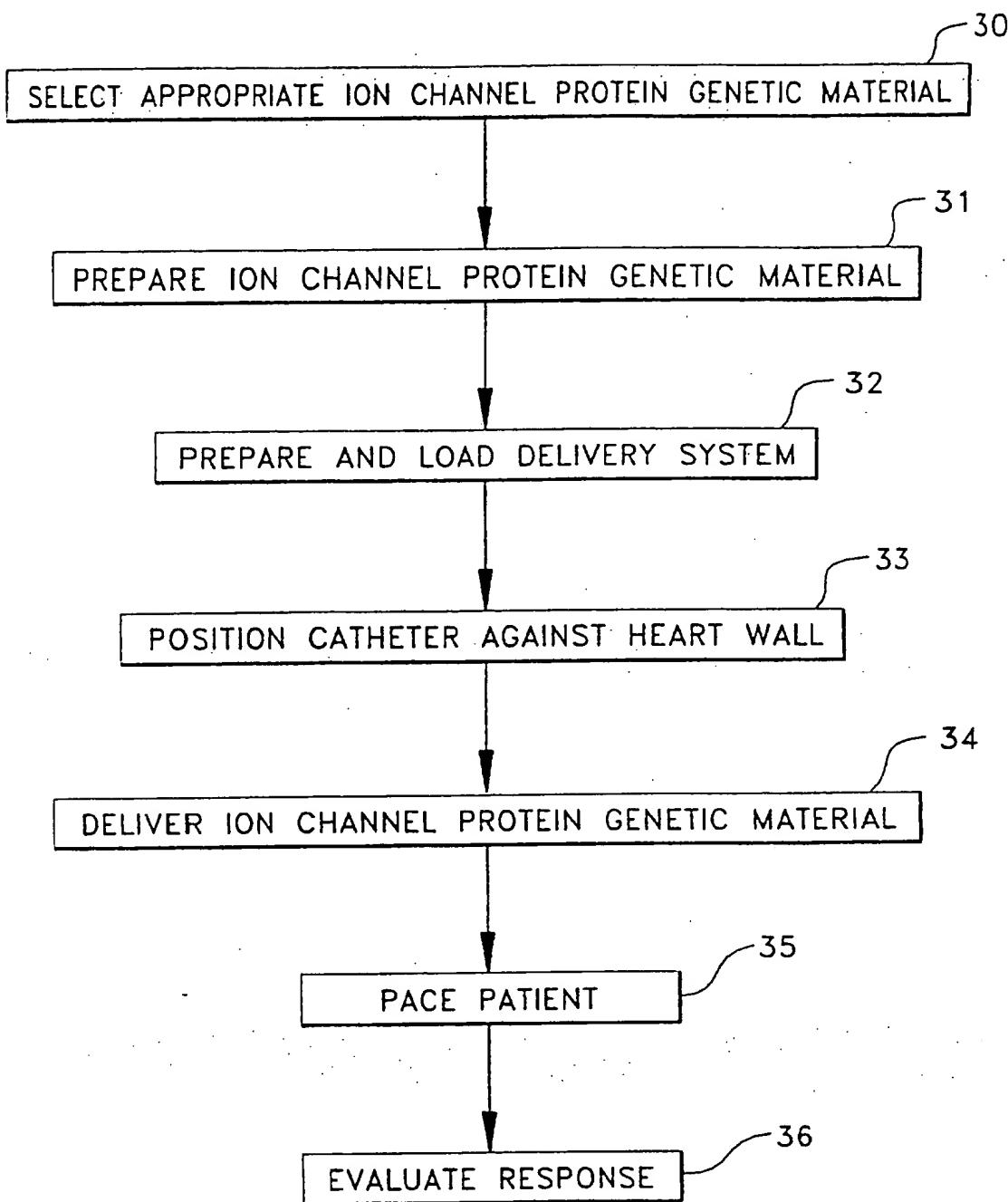


FIG. 1

2/5

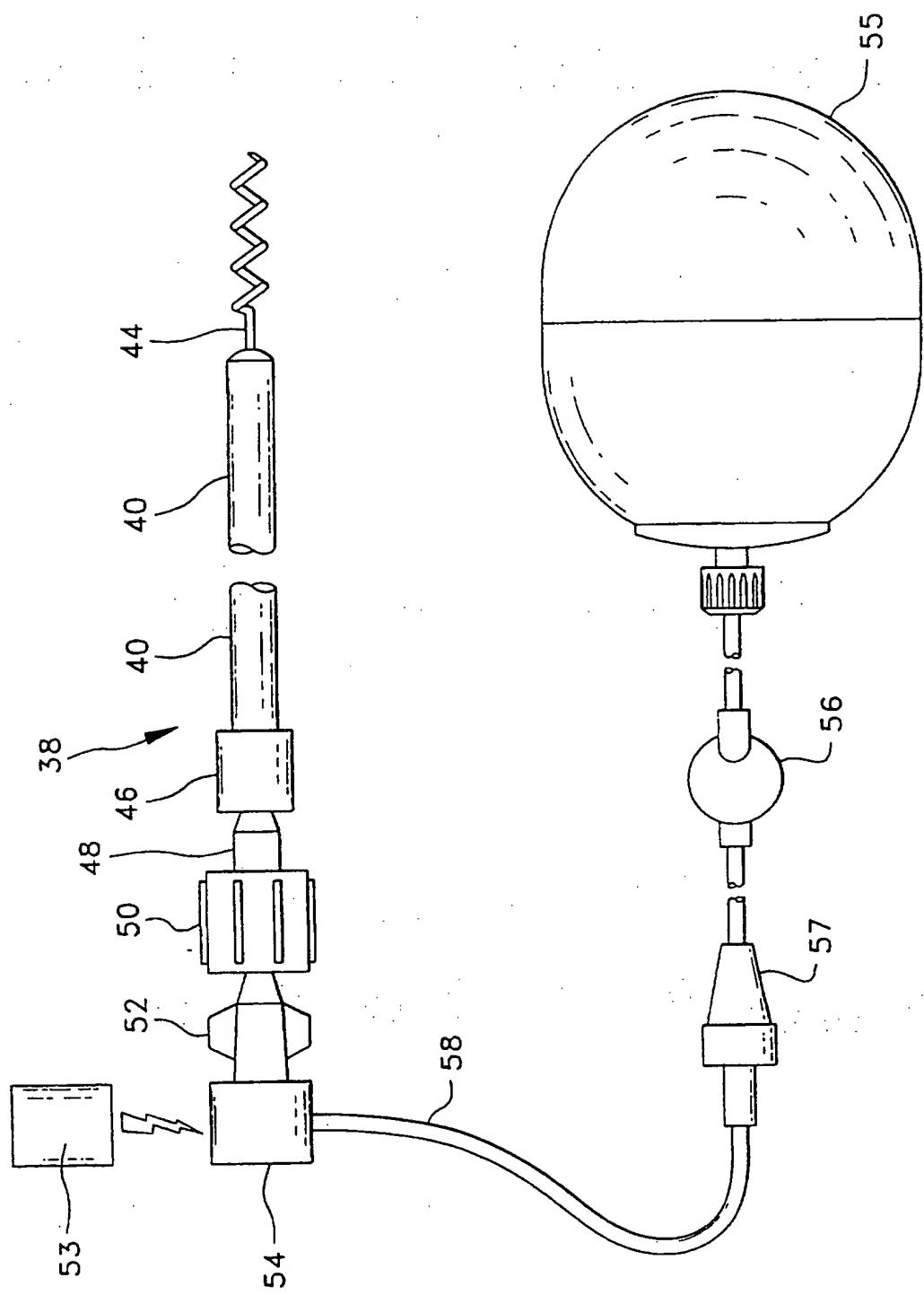
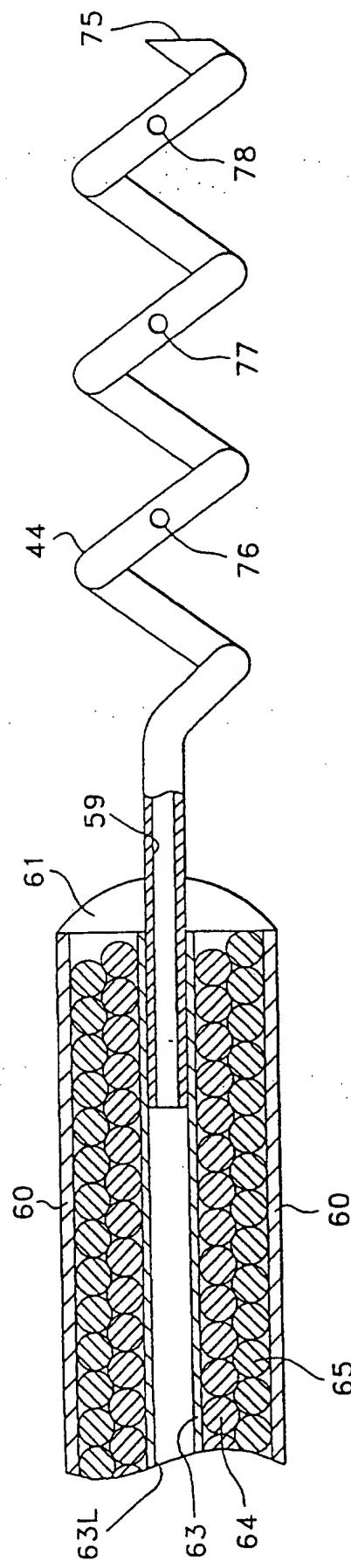
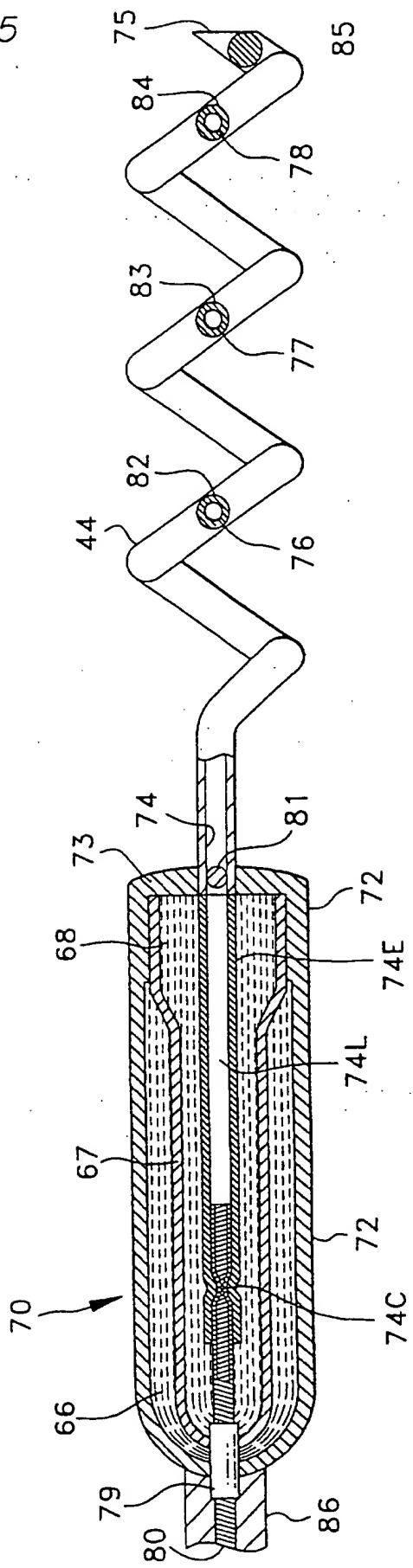


FIG. 2



3/5



4/5

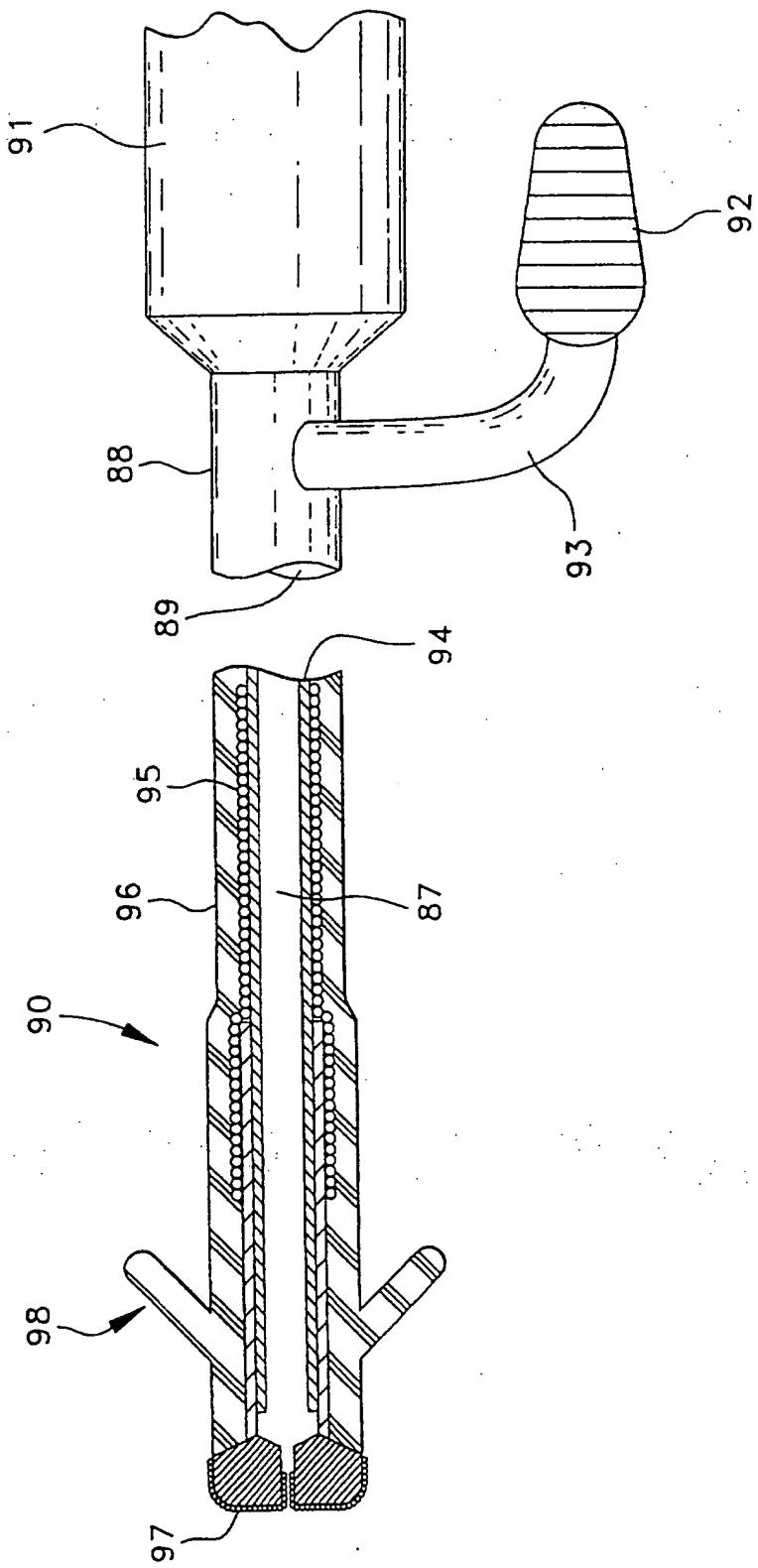


FIG. 5A

5/5

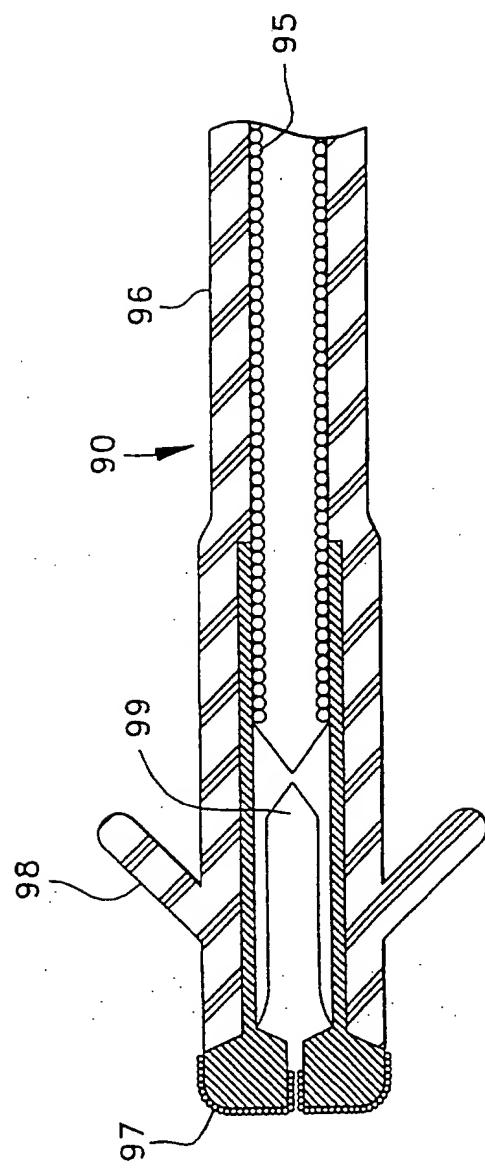


FIG. 5B

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/05556

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.  
 US CL :514/44; 536/23.1; 435/320.1; 607/120  
 According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 536/23.1; 435/320.1; 607/120

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG: MEDLINE, BIOSIS, EMBASE, DERWENT; APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,496,360 A (D.A.HOFFMAN) 05 March 1996, see abstract	1-35
Y	US 4,711,251 (K.B. STOKES) 08 December 1987, see abstract	1-35
Y	NABEL et al. Recombinant Gene Expression in Vivo Within Endothelial Cells of the Arterial Wall. Science. Vol. 244, pages 1342-1344, see entire document.	1-35
Y	GELLENS et al. Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. Proc. Natl. Acad. Sci. USA. January 1992, Vol. 89, pages 554-558, see entire document.	1-35

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
12 MAY 1997	12 JUN 1997

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ABDUR RAZZAQUE Telephone No. 703-308-0196
Faxsimile No. (703) 305-3230	

PCT/USA/0212 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/05556

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A01N 43/04; A61K 31/70; C07H 21/02, 21/04; C12N 15/00, 15/09, 15/63, 15/70, 15/74; A61N 1/04